Vitamin D in Pregnancy and Lactation in Humans

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Abstract

Concerns exist about the adequacy of vitamin D in pregnant and lactating women. This review assesses the evidence that maternal vitamin D status influences maternal, fetal, and breast-fed infant bone health; maternal adverse outcomes (preeclampsia, gestational diabetes, obstructed labor, and infectious disease); fetal adverse outcomes (growth, gestational age, and developmental programming); and infant adverse outcomes. The evidence for all of these outcomes is contradictory (except for maternal infectious disease) and lacking causality; thus, it is inconclusive. The 2011 Dietary Reference Intakes for vitamin D and their implications for assessing vitamin D status are discussed. An estimated 5% to 29% of American pregnant women may have inadequate vitamin D status, with the higher prevalence in African Americans. Little is known about the prevalence of inadequacy in American lactating women. Research needs are also identified, especially the need for rigorous and well-designed randomized clinical trials to determine the role of vitamin D in nonbone health outcomes in pregnancy and lactation.

Contents

INTRODUCTION

Pregnancy and lactation are dynamic periods for bone health. The understanding about how maternal vitamin D levels affect health outcomes in the mother, fetus, and breast-fed infant continues to evolve. Indeed, the specific role that vitamin D plays in successful pregnancy, lactation, and fetal or early infant development is unclear (66). Concerns exist, however, given the importance of its classical role in bone health and its potential association with nonbone health outcomes as well as the developmental programming of offspring's health. Globally, vitamin D–deficient rickets in infants and children remains prevalent, ranging from 9% to 70% in Asia, the Middle East, and Africa, and is reemerging in developed countries in ethnically diverse, dark-skinned and prolonged breast-fed individuals without vitamin D supplementation (108). Vitamin D deficiency in pregnant women is a concern because low serum 25-hydroxyvitamin D levels, a biomarker of exposure, range from 5% to 84% globally (18, 108, 130), but the prevalence in lactating women is less understood. Considered below, after a brief introduction, is our current understanding of vitamin D metabolism, function, maternal and fetal health outcomes, dietary requirements, and status[1] in pregnancy and lactation as well as the gaps in our knowledge and research needs.

Vitamin D, a seco-sterol, can be consumed from the diet or produced endogenously in the skin. Two forms exist—vitamin D_2 (ergocalciferol), which is used as a food fortificant or supplement, and vitamin D_3, which is produced endogenously. Their bioequivalency (reviewed in 66) is not well established even though both exhibit antirachitic bioactivity. Only a few foods, such as fatty fish, are rich in vitamin D_3, but a growing number of foods are fortified with vitamin D_2 or D_3, including milks (cows, soy, and rice) and some yogurts, ready-to-eat cereals, margarines, and fruit juices (141).

Once ingested, vitamin D is absorbed by enterocytes, packaged into chylomicrons, released through the lymph into the peripheral blood, and transported to the liver in the resulting remnant particles. Exposure of skin to solar UV B radiation (290–320 nm) converts 7-dehydrocholesterol to previtamin D, which then isomerizes to vitamin D_3 and, once released into the blood, binds to vitamin D binding protein (DBP), which transports it to the liver. Vitamin D, irrespective of source or form, is biologically inactive and must be activated by two sequential hydroxylations to 1,25 dihydroxyvitamin D [1,25$(OH)_2$D]. The first hydroxylation in the liver by 25-hydroxylase (most likely CYP2R1) results in 25-hydroxyvitamin D (25OHD), which binds to DBP once released into the blood (**Figure 1**; 70). The second hydroxylation occurs in the kidney,

[1] Status refers to the adequacy of nutrient intake or exposure relative to requirements. In the case of vitamin D, serum 25-hydroxyvitamin D, a biomarker of total exposure from dietary intakes and endogenous production, is used to assess adequacy.

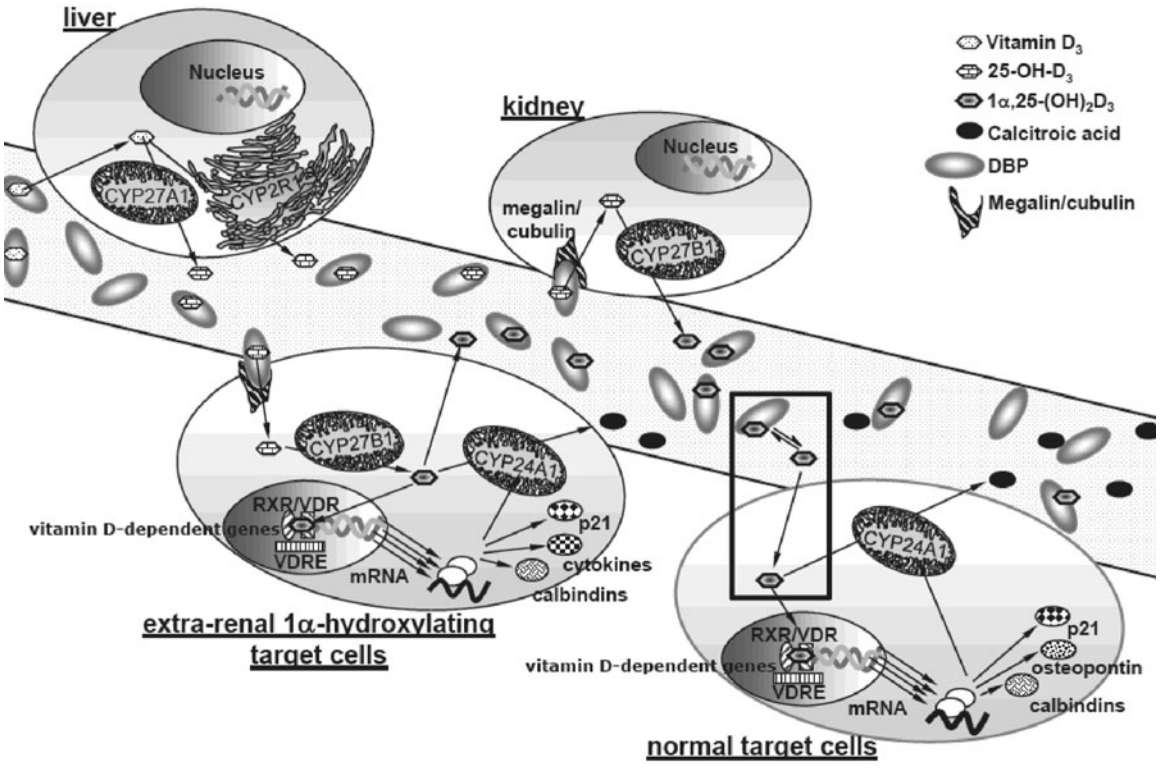

Figure 1

Vitamin D metabolism, transport, and mechanism of action. Most components of vitamin D signal transduction are illustrated. Vitamin D_3 (*upper left*) is carried to the liver, where one of a series of 25-hydroxylases—the major ones are the microsomal CYP2R1 and the mitochondrial CYP27A1—activates it. The resulting 25-hydroxyvitamin D_3 [$25(OH)D_3$] is then carried on vitamin D binding protein (DBP) to the kidney, where the classic renal CYP27B1 1-α hydroxylates it and puts it back into circulation as 1α,25-dihydroxyvitamin D_3 [$1\alpha,25(OH)_2D_3$]. Next, $1\alpha,25(OH)_2D_3$ enters and acts on vitamin D target cells at the level of gene transcription through a VDR-mediated mechanism (*bottom right*). Note that according to this vitamin D signal transduction, $1\alpha,25(OH)_2D_3$ arrives at the target cell bound to DBP, but its entry into the cell is a function of the free pool of $1\alpha,25(OH)_2D_3$ (shown inside the box) in equilibrium with protein-bound $1\alpha,25(OH)_2D_3$. According to the extrarenal 1α-hydroxylase theory, some target cells express the membrane proteins megalin or cubulin to concentrate the $25(OH)D_3$-DBP complex and express the protein CYP27B1 to 1α-hydroxylate 25(OH)D. RXR, retinoid X receptor; VDR, vitamin D receptor; VDRE, vitamin D responsive element. (Adapted from Reference 70; reprinted with permission from *Am. J. Clin. Nutr.*)

by 1-α-hydroxylase (CYP27B1) under the countervailing regulation of parathyroid hormone (PTH) or fibroblast growth factor 23 (FGF 23) in response to calcium and phosphate levels, respectively (66, 108). Thus, the metabolism of vitamin D interrelates with that of calcium and phosphate (**Figure 2**; 110). Briefly, low levels of serum calcium stimulate the release of PTH, which stimulates renal activation of $1,25(OH)_2D$ and results in increased intestinal calcium absorption, renal reabsorption, and bone calcium resorption to restore serum calcium levels. In contrast, high serum phosphate levels stimulate the release of FGF23 from bone, which reduces renal activation of $1,25(OH)_2D$ and, thus, intestinal phosphate absorption, increases renal phosphate secretion, and enhances catabolism of $1,25(OH)_2D$ and 25OHD. Renally produced $1,25(OH)_2D$ also binds to DBP, once it is released into the blood.

In a wide variety of cells, $1,25(OH)_2D$ binds its nuclear receptor, vitamin D receptor (VDR), and thereby regulates transcription of a diverse array of genes that maintain

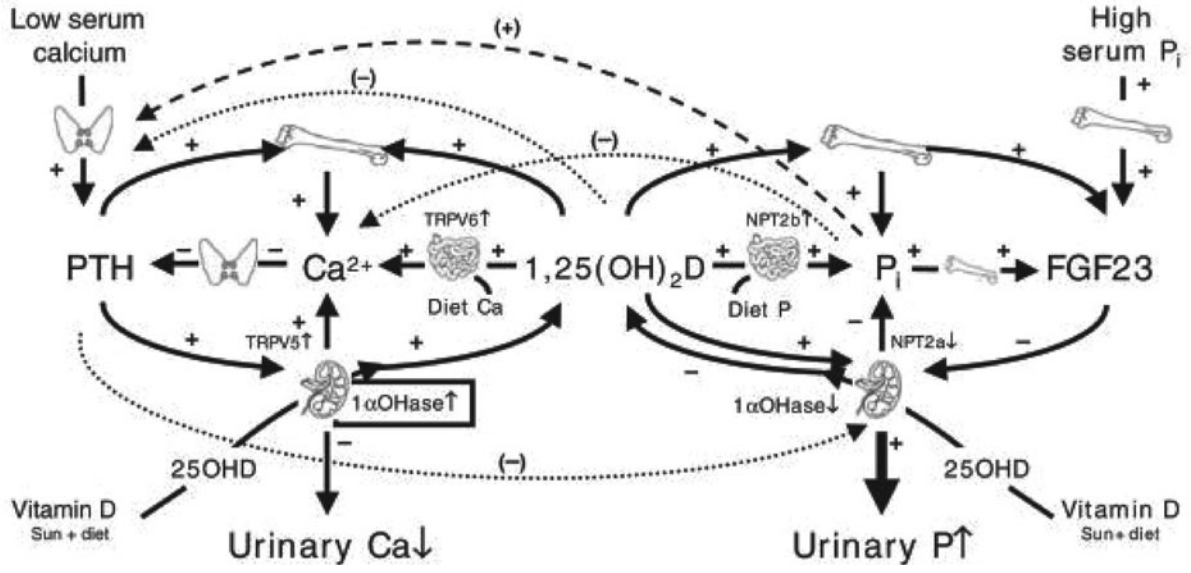

Figure 2

A proposed schematic for an integrated calcium-phosphate-vitamin D homeostatic system. PTH, parathyroid hormone; 25OHD, 25-hydroxyvitamin D; TRPV5, TRPV6, transient receptor potential cation channel subfamily V, member 5 and 6, respectively; 1αOHase, 25-hydroxyitamin D-1α-hydroxylase; NTP2a, NTP2b, Na-phosphate cotransporters; FGF23, fibroblast growth factor 23; P_i, inorganic phosphate; +, increased; -, decreased. (From Reference 110; reprinted with permission from *Proc. Nutr. Soc.*)

calcium and phosphate homeostasis and bone mineralization through the classic vitamin D endocrine system. It also modulates cellular growth, differentiation, and immune function (reviewed in 66). Many extrarenal tissues also express 1-α-hydroxylase and can produce $1,25(OH)_2D$ in vitro. Thus, local intracrine, paracrine, or autocrine action of $1,25(OH)_2D$ is feasible but has not yet been demonstrated in vivo. $1,25(OH)_2D$ and 25OHD are catabolized to inactive calcitroic acid and 24,25dihydroxyvitamin D [$24,25(OH)_2D$], respectively, by 24-hydroxylase (CYP24A1) located in the kidney and many other tissues. Catabolism is regulated by $1,25(OH)_2D$ and FGF23 (reviewed in 34, 66).

Because of its longer half-life and reflection of both dietary and endogenous sources, circulating 25OHD is the best biomarker of exposure to vitamin D. Its usefulness as a biomarker of effect has not been validated, nor are there evidence-based consensus guidelines on its interpretation for assessing vitamin D status (66). Although various cut-points have been suggested for determining vitamin D deficiency, insufficiency, and sufficiency, the 2011 Institute of Medicine (IOM) Dietary Reference Intakes (DRI) for vitamin D (discussed below) link serum 25OHD levels ≥50 nmol/L[2] with the Recommended Dietary Allowance (RDA) that meets 97.5% of the population's need and a level of <30 nmol/L with increased risk for vitamin D–deficient rickets. Serum $1,25(OH)_2D$ levels are generally not a useful reflection of exposure due to their short half-life.

VITAMIN D AND PREGNANCY

Physiologic Changes

Key physiological changes in the pregnant woman affect maternal transport and

[2] To convert 25OHD levels from nmol/L to ng/ml, divide by 2.5.

metabolism of vitamin D, although the specific mechanisms underlying these changes are not fully understood. Cumulatively, these changes increase the circulating levels of DBP and serum $1,25(OH)_2D$, with little effect on serum 25OHD levels (102). The relative contributions of the kidney and placenta to these changes remain unknown. Both 25(OH)D and $1,25(OH)_2D$ transfer across the perfused human placenta (114). Generally, cord blood 25OHD levels are 75% on average of maternal serum levels and correlate with them (20, 49, 67, 128), whereas cord blood $1,25(OH)_2D$ levels are less (52% on average) and do not correlate with maternal serum levels (20, 49, 67, 128) but are similar to those found in nonpregnant controls. The correlation of cord and maternal serum 25OHD suggests that 25OHD may be the predominant metabolite transferred to the fetus in humans.

DBP. DBP increases 7% to 152% during pregnancy, as reported in four cross-sectional (6, 10, 20, 50) and two longitudinal studies (113, 140). How early DBP levels increase in pregnancy is best determined from the single longitudinal study from prepregnancy through lactation (113) in which DBP increases at 8–10 weeks (the earliest time measured). How quickly DBP levels return to prepregnant values postpartum is also not well established. DBP decreases within two weeks postpartum, reaching nonpregnant control levels by six weeks (140), but the nonpregnant reproductive-aged controls in this study were significantly older than the postpartum women. DBP levels are comparable to prepregnant levels by three months postpartum in the prepregnant longitudinal study, but earlier postpartum times were not examined (113). The mechanism whereby circulating DBP levels increase in pregnancy is unknown, but regulation by estrogen has been suggested (6, 50). Some evidence supports a role for estrogen, including higher serum levels of DBP in women taking oral contraceptives (50, 134) and in peri- and postmenopausal women treated with oral estrogen (11, 39).

Vitamin D metabolites. Maternal serum $1.25(OH)_2D$ levels increase, whereas serum 25OHD levels or $24,25(OH)_2D$ levels do not, as reported by 11 longitudinal studies, 2 randomized clinical trials (RCTs), and 17 cross-sectional studies; of these, 24 are included in a recent meta-analysis (102), and 6 are not (35, 67, 100, 116, 140, 144). Only one cross-sectional study conducted in pregnant Nigerian adolescents does not report an increase in serum $1,25(OH)_2D$ levels compared to nonpregnant controls (116). In this meta-analysis, serum $1,25(OH)_2D$ levels increase 104% at term with no change in serum 25OHD, which increases the ratio of serum $1,25(OH)_2D$ to 25OHD (**Figure 3**; 102). In the six studies not included in this meta-analysis, serum $1,25(OH)_2D$ levels increase 134% in pregnancy. Furthermore, serum 25OHD levels are unaffected by pregnancy, except in one longitudinal study (35) and one cross-sectional study (116) in which levels increase in the third trimester. Thus, inclusion of these additional studies is unlikely to change the conclusion but might slightly affect the magnitude of the increase in serum $1,25(OH)_2D$ levels in pregnancy.

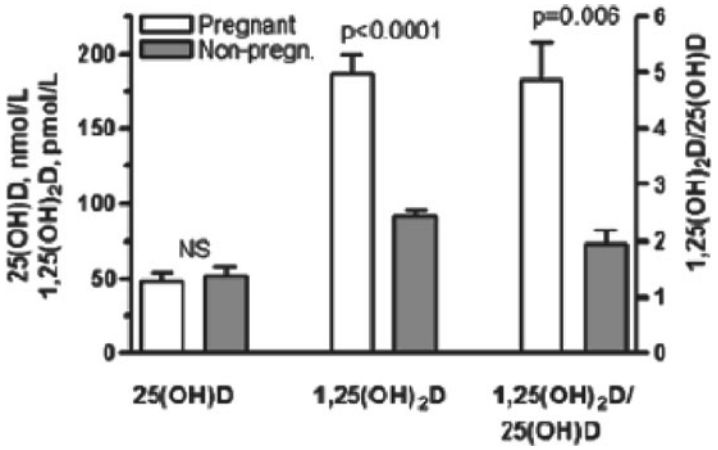

Figure 3.

Comparison of the grand means (± SEM) of serum 25(OH)D (nmol/L), of serum $1,25(OH)_2D$ (pmol/L), and of the ratio of $1,25(OH)_2D/25(OH)D$ between pregnant (n = 20 studies) and nonpregnant (n = 9 studies) young women. NS, not significant. [Adapted from Reference 102; reprinted with permission of *Hormones* (*Athens*)].

Despite the strong concordance of these data, only two studies (35, 113) examine longitudinally the changes in all the vitamin D metabolites, and a third study (94) examines the change in 25OHD prior to pregnancy through postpartum. A limitation in most of the longitudinal studies from early pregnancy to term or early postpartum is the use of a nonpregnant comparator group that typically is not matched for age or prepregnant body mass index (BMI), which influences maternal serum 25OHD levels. In some longitudinal studies, postpartum comparisons are used to assess changes in pregnancy although it is not known whether all physiologic changes have been restored to prepregnant levels. Only a few studies consider seasonal variation in serum 25OHD levels in the design or analyses, which is a particular concern in cross-sectional studies. Furthermore, many of these longitudinal or cross-sectional studies do not consider usual dietary calcium intakes. Only two consider dietary phosphate intake, and they report contradictory results—a 28% increase during pregnancy (35) or no change (113). However, dietary calcium and phosphate may interact with vitamin D metabolism. Nonetheless, the results are consistent in finding that maternal serum $1,25(OH)_2D$ levels double during pregnancy.

How early this change in serum $1,25(OH)_2D$ occurs is best assessed in the longitudinal studies from prepregnancy through lactation (35, 113), which have differing results. In one (35), serum $1,25(OH)_2D$ levels increase approximately 47% by 10–12 weeks and continue increasing until 22–24 weeks, then remain elevated to term, and return to prepregnancy levels by three months postpartum (the earliest period measured). In the second (113), serum $1,25(OH)_2D$ levels do not increase in the first 8–10 weeks, but increase by 23–26 weeks. Taken together, these results suggest that serum $1,25(OH)_2D$ levels increase between 10 and 12 weeks, but not earlier. Other longitudinal studies also report increased serum $1,25(OH)_2D$ levels during the first trimester compared to postpartum levels or nonpregnant controls (46, 100, 133, 144).

Serum $1,25(OH)_2D$ and serum 25OHD levels are not correlated, but serum $24,25(OH)_2D$ and serum 25OHD levels are ($r^2 = 0.42$) based on a meta-regression analysis (102). Few details are provided for the meta-regression analyses, including the heterogeneity among the studies. Given the different analytical methods for 25OHD (competitive binding protein assay, radioimmunoassay, or high-pressure liquid chromatography), the variability among methods and analysts and the fact that many of these studies predate the now available National Institute of Standards and Technology Standard Reference Material for serum 25OHD levels or the Vitamin D External Quality Assessment Scheme, considerable heterogeneity among studies is expected in the serum 25OHD levels. Consideration of study heterogeneity would have strengthened this meta-analysis.

Papapetrou (102) discusses the implications that a sustained high serum $1,25(OH)_2D$ level during pregnancy does not appear to impact either 25OHD or $24,25(OH)_2D$, which might be expected given its regulation of 24-hydroxylase. How the metabolic flux of vitamin D is altered in pregnancy and why $1,25(OH)_2D$ does not appear to affect the catabolism of 25OH is difficult to discern with only static measures of circulating metabolites.

Whether the increase in serum $1,25(OH)_2D$ levels follows the increase in DBP has been speculated; the limited evidence from a total of 23 women (35, 113) suggests that it does. DBP increases at 8–10 weeks (113), prior to the increase in serum $1,25(OH)_2D$ levels at 10–12 weeks (35). One might expect that 25OHD would be similarly increased if the rise in DBP causes the increase in $1,25(OH)_2D$, but it is not. Furthermore, free $1,25(OH)_2D$ levels also increase 37% to 69% during pregnancy (10, 113, 140) and return to nonpregnant control values two weeks postpartum (140). The temporal changes in free $1,25(OH)_2D$ levels have been assessed in only one longitudinal study, prepregnancy to postpartum, in 12–14 women (113). By 8–10 weeks, free $1,25(OH)_2D$ levels are not significantly different from either prepregnancy or elevated values near term;

thus, a slight increase of 25% in mid-first trimester, though not significant, is noted. Researchers need to determine the mechanism whereby maternal serum $1,25(OH)_2D$ levels selectively increase without effect on the other key metabolites, the interaction with the increase of DBP, and the possible role of estrogen. Overall, the increase in total and free serum $1,25(OH)_2D$ levels, even with the increase in DBP, suggests a greater potential delivery of active vitamin D to tissues during pregnancy by late in the first trimester and is sustained through the end of gestation.

Which tissues produce the additional circulating $1,25(OH)_2D$ is not certain because of the possible contributions from the placenta and decidua, which express 1-α-hydroxylase mRNA at 100- and 1,000-fold higher levels, respectively, in the first and second trimester than in the third trimester (143). The enzyme is more strongly located (by immunostaining) in villous syncytiotrophoblasts than in the underlying cytotrophoblasts in the first and second trimester (143). Decidual stromal cells strongly exhibit the enzyme. Primary cultured placental trophoblasts also express 1-α-hydroxylase mRNA (38), as do primary cultured decidual cells from early pregnancy (135). In vitro, both placental (53, 139) and decidual cells (139) synthesize $1,25(OH)_2D$ and $24,25(OH)_2D$ from ^{3}H-25OHD.

Recently, a placental-specific methylation of 24-hydroxylase was identified (98) that reduces basal expression of the mRNA and prevents regulation by $1,25(OH)_2D$. Thus, placentally produced $1,25(OH)_2D$ in humans may not be easily catabolized in situ and potentially could be released into the maternal compartment.

However, the importance of renal contribution in elevating maternal serum $1,25(OH)_2D$ levels is suggested by a case report in a nephrotic pregnant woman who received oral $1,25(OH)_2D$ prior to conception until 21 weeks gestation, when treatment was discontinued until delivery at 24 weeks because of hypercalcemia (132). Her serum $1,25(OH)_2D$ levels did not increase from conception to 21 weeks gestation but also did not decrease after treatment was discontinued. This limited evidence suggests that although the kidney contributes to serum $1,25(OH)_2D$ levels during pregnancy, nonrenal tissues may also contribute. The role of the placenta in the physiologic elevation of $1,25(OH)_2D$ needs to be elucidated.

PTH. The effects of pregnancy on serum PTH levels are contradictory and inconsistent. No change is reported from prepregnancy through postpartum (113) or from the second trimester through postpartum (133). In contrast, increases are reported in other longitudinal studies from the second to third trimester (28%), with a further increase (83%) postpartum (120) and from prepregnancy through postpartum (36%; 94). Thus, conclusions about pregnancy and PTH or the relationship to serum 25OHD levels are difficult to draw.

Maternal and Fetal Functional and Health Outcomes

Maternal bone health. Bone turnover in pregnancy is controversial (for a recent review, see 66), and its relationship to maternal serum 25OHD levels is unclear. The 2007 Agency for Healthcare Quality Research (AHRQ) systematic evidence–based review (33) finds insufficient evidence to assess this relationship. Conflicting reports exist on bone turnover during pregnancy that is assessed by changes in bone mineral density (BMD) and measured by dual-energy X-ray absorptiometry (DEXA), single-photon absorptiometry, or serum biomarkers. The following discussion focuses on those longitudinal studies, which are prepregnancy to postdelivery or early postpartum to avoid the limitation of a long pre- or post-pregnancy period and factors other than pregnancy (66). Furthermore, only studies in which calcium intakes were 700 mg/day or greater are discussed because of the correlation of the serum bone resorption markers [carboxyterminal C-telopeptide cross-linked of type I collagen (CTX) and urinary aminoterminal cross-linking region of type I collagen telopeptide (NTX)] with calcium intakes, which suggests

that skeletal response may be influenced by low calcium intakes (144). In two studies, pregnancy does not affect BMD of the dominant arm (35), integral total or component region BMD, and total bone mineral content (BMC; 113) or trabecular spinal BMD (113). In contrast, trabecular BMD decreases during pregnancy (12, 93, 105), but cortical BMD does not (105). In one study, serum bone formation markers increase 96% for osteocalcin, 290% for bone-specific alkaline phosphatase (BSAP), and 649% for procollagen 1 carboxy peptidase (P1CP), whereas a bone resorption marker, urinary deoxypyridinoline crosslinks (DPyr), increases only at delivery and not during gestation (94). In contrast, another study (12) reports increased DPyr by 14 weeks with further increases throughout pregnancy, but no increase until late in pregnancy for BSAP and P1CP. Thus, it remains unclear to what extent bone mineral is mobilized during pregnancy. Furthermore, in the two studies that measured serum 25OHD levels, BMD is unaffected (35, 113). Thus, no information is available on the impact of vitamin D status on maternal bone health during pregnancy. However, the studies to date may not have been sufficiently powered to assess variable and dynamic bone turnover during pregnancy.

Osteoporosis associated with pregnancy, although rare, has been documented in case reports (106, 123, 124, 131). Typically, patients present in the third trimester or early in lactation with back pain, vertebral fractures, and very low BMD. The causes are largely unknown, but one report raises possible genetic components associated with low peak bone mass in affected related females (106). The relationship to vitamin D status is also unclear because only two case reports measured serum 25OHD levels. In one report, all five cases have serum 25OHD levels <50 nmol/L, with three ≤ 25 nmol/L, and two have serum $1,25(OH)_2D$ levels that are lower than 50 pmol/L (124). In the second report, only one of three cases has low serum 25OHD levels (12 nmol/L); the other two have high levels of serum 25OHD levels (80–97 nmol/L; 131). No clear association of pregnancy-associated osteoporosis and vitamin D exists.

Maternal calcium absorption. A key physiologic change in pregnancy is the doubling of fractional calcium absorption (58), but that vitamin D plays a role in this change is unlikely despite the association of similar temporal changes in serum $1,25(OH)_2D$ and calcium absorption (113). Relevant animal studies in vitamin D–deficient rats (23, 56) and *Vdr*-null mice (44) demonstrate that vitamin D is not required for the physiologic change in calcium absorption in pregnancy.

Fetal bone health. The relationship of maternal vitamin D status to fetal bone health is difficult to assess in light of the paucity of available RCTs and the contradictory reports from observational studies summarized below. The IOM DRI Committee (66) noted and reviewed relevant animal studies in vitamin D deficiency and *Vdr*-null mice that suggest that vitamin D is not required for normal developmental and skeletal outcomes or placental-fetal transfer of Ca. Furthermore, Bouillon and colleagues (21) comment that the skeleton seems normal at birth in humans with a genetic absence of functional VDR or 1-α-hydroxylase and in whom severe vitamin D–resistant rickets develops subsequently. Thus, even the role of vitamin D in skeletal development and mineralization is uncertain.

Skeletal development and mineralization and its relationship to maternal vitamin D status are reported in only one RCT and eight observational studies, excluding case reports on congenital rickets, which are discussed below. The results are mixed, with half reporting no relationship and half reporting an inverse relationship. The only RCT (24) reports no effect of 1,000 IU/day[3] of vitamin D in the third trimester in Asian women, compared to placebo-treated controls, on neonatal

[3]To convert vitamin D in IU to μg, divide by 40.

crown–heel length, forearm length, or head circumference, although fontanelle area decreases 33% with vitamin D treatment. One perplexing aspect of this study, however, is the achieved maternal serum 25OHD level (168 nmol/L) that is much higher than would be expected with the stated dose, which suggests that the actual dose received may have been considerably higher than stated. No relationship of maternal serum 25OHD levels with neonatal BMC (by DEXA) is observed in a cross-sectional study of Turkish women (1) or in a secondary analysis study in Gambia (109). Another observational study reports no effect on neonatal BMC of the right forearm with 1,000 IU/day of maternal vitamin D supplemental use and no relationship with serum 25OHD levels (32).

In contrast, five observational studies using different assessment methods report an inverse relationship of maternal serum 25OHD levels with an aspect of skeletal development or mineralization (81, 95–97, 137). In a prospective cohort study using high-resolution 3D ultrasound imaging, maternal serum 25OHD levels inversely correlate with fetal femur cross-sectional area ($r^2 = -0.025$ and -0.01 at 19 and 34 weeks, respectively) and femoral splaying index (cross-sectional area/length; $r^2 = -0.029$ and -0.012 at 29 and 34 weeks, respectively) (81). A cross-sectional study using quantitative computed tomography (137) reports 9% lower tibia BMC in neonates with maternal and cord blood 25OHD levels <42.6 nmol/L and a correlation of maternal postpartum serum 25OHD levels with tibia BMC (adjusted for birthweight Z score) and cross-sectional area ($r^2 = 0.054$ and 0.046, respectively). Of note, maternal calcium and vitamin D intakes are high (1,750 mg/day and 600 IU/day, respectively) because 80% of participants used supplements. Similarly, total BMC (by DEXA) and cord blood 25OHD levels are lower (8% and 65%, respectively) in Korean infants born in the winter compared with those born in the summer (97). Total BMC correlates with serum 25OHD levels ($r^2 = 0.059$). Knee–heel length, but not crown–heel length, correlates inversely with serum 25OHD levels and is reduced with maternal serum levels (<28 nmol/L; 95, 96).

Congenital rickets consequent to severe maternal vitamin D deficiency or hereditary rickets typically results in normal neonatal skeleton but rapid onset of rickets 2–7 days or a few months after birth (reviewed recently in 66). However, several case reports of severe maternal vitamin D deficiency and osteomalacia exist. In one, radiological evidence of some skeletal abnormalities and reduced bone ash with normal Ca/P ratios is reported in seven fetuses even though normal "centers of ossification" are present (88). Wrist ossification centers vary by season and latitude in China at 3 to 5 days old and are reported more likely to be present in southern neonates and neonates born in the fall, when cord 25OHD levels are higher (126). In four cases of Middle Eastern or Turkish women (104) with osteomalacia, their neonates had some evidence of skeletal effect, including craniotabes (4/4 at days 3 to 12) and a rare abnormality in the left radius that had fractured at day 12 (1/4). Neonatal and maternal serum 25OHD levels were also low (9.3 to 25 nmol/L and 6.3 to 29 nmol/L, respectively; 4/4). Exemplifying that not all cases of congenital rickets stem from severe maternal primary vitamin D deficiency, however, is the case report of two neonates presenting with congenital rickets within one day of birth (9) due to maternal malabsorption and not maternal osteomalacia. The evidence on congenital rickets is frequently limited by lack of information on the vitamin D status of the mother, particularly in the early reports; confounding maternal malnutrition or malabsorption; lack of information about the neonate's skeletal health immediately at birth; and lack of information on maternal calcium status. What is clear is that very severe maternal vitamin D–deficient osteomalacia predisposes neonates to develop early-onset neonatal rickets. Whether coincident maternal calcium insufficiency contributes to congenital rickets needs to be determined.

Hypocalcemia is also reported in neonates born to severely vitamin D–deficient women and again does not typically present at birth but

rather a few days later (8, 26). Neonatal serum calcium drops at day four after birth in normal neonates with or without vitamin D supplementation (36). This physiological postnatal change may become more severe and life threatening when the neonate has low 25OHD levels consequent to severe maternal vitamin D deficiency.

Summary. The importance of maternal vitamin D status to fetal skeletal development and bone health in the newborn is unclear because of contradictory evidence on the relationship of maternal vitamin D status and fetal skeletal development and mineralization. In extreme maternal vitamin D–deficient osteomalacia, the neonate is at risk for neonatal rickets and hypocalcemia within days of birth. The interrelationship of maternal calcium status and polymorphisms that may alter vitamin D metabolism are important to elucidate and may explain some of the contradictory evidence that presently exists.

Maternal adverse outcomes beyond bone health. Other adverse maternal health outcomes beyond bone health considered in association with maternal vitamin D status include preeclampsia (PE), obstructed labor and C-section, gestational diabetes mellitus (GDM), and infectious disease. The most studied of these is PE, a pregnancy-induced hypertension with proteinuria occurring after 20 weeks of gestation, with a prevalence of 5% to 10% globally. Its etiology is unknown, but impaired placentation is proposed as a key intrinsic etiologic factor (for recent reviews, see 30, 65) leading to endothelial cell dysfunction. Delivery of the placenta after the birth resolves PE, which emphasizes its role in this disorder. Additionally, maternal systemic factors may also result in PE through inadequate maternal response to the placenta (65). A role for maternal vitamin D status in PE has been hypothesized since the early 1990s (22), but its mechanism is not known. Most frequently suggested is its regulation of maternal and placental immune responses and cytokines, which could also protect against maternal infections. Indeed, a role for vitamin D in the regulation of anti-infective components of the immune system is biologically plausible, as evidence from in vitro and some animal models demonstrate (for a recent review, see 60). A role for vitamin D in β-islet function is also biologically plausible, as demonstrated by evidence from animal models and molecular studies (for a recent review, see 76).

Only observational studies are available, except for PE, for which one nonplacebo controlled RCT conducted in India is available. Most of the observational studies have not considered maternal calcium or phosphate intakes, which could interrelate with vitamin D metabolism during pregnancy. Many have not considered seasonal variation or other potential confounders. Furthermore, for most outcomes (with the exception of infectious disease) the evidence is also contradictory across the studies, as discussed below. Overall, the evidence on maternal adverse nonbone health outcomes and vitamin D is contradictory and lacks causality; thus, the role of vitamin D and the relationship of maternal vitamin D status to nonbone health outcomes is presently inconclusive.

PE has been associated with maternal vitamin D status, but the evidence is contradictory. One RCT (87), one prospective cohort study in pregnant women at increased risk of PE (122), four prospective nested case-control studies (5, 14, 55, 107), and seven case-control studies (4, 42, 51, 52, 54, 74, 121) are reported. The RCT, conducted in India, finds no difference in PE with 1,200 IU of vitamin D with 375 mg calcium daily, but it finds a small decrease of 8 mm Hg in diastolic blood pressure with treatment (87). Of the prospective cohort and nested case-control studies, three find no association or increased risk (55, 107, 122), whereas two find an increased risk (5, 14) of PE with low maternal serum 25OHD levels. The risk of severe PE (defined as a higher blood pressure/proteinuria than the diagnostic criteria) increases with lower serum 25OHD levels <50 nmol/L (OR $= 5.4$; $p < 0.001$; 5). The risk of PE increases 2.4 fold for every serum 25OHD-level decline of 50 nmol/L (14). Case numbers are lower by 19% among

the studies reporting no relationship (28 to 39) and those reporting increased risk (43–55) with low maternal serum 25OHD levels. Median or mean serum 25OHD levels, however, are similar across these studies (42–70 nmol/L in those not reporting a relationship, and 45–98 nmol/L in those reporting increased risk). The case-control studies also report conflicting results. Two case studies (42, 121) find no difference in serum 25OHD levels between PE cases and controls, with median levels from 59 to 89.8 nmol/L. These two and the remaining case studies all report significantly lower (67%) serum $1,25(OH)_2D$ levels in PE cases compared with controls.

Overall, the evidence concerning the relationship of maternal vitamin D status with risk of PE is inconclusive. The most consistent observation comes from case studies in which maternal serum $1,25(OH)_2D$ levels are reduced, but caution is needed in interpreting this finding. Abnormal placentation, known to occur in PE and postulated to play a causative role in its etiology, might adversely impact placental production or catabolism of $1,25(OH)_2D$ and any contribution such production makes to circulating levels.

Obstructed labor and C-section in relation to maternal vitamin D status is examined in only two observational studies (25, 91), which have contradictory findings. In a case-control study in Pakistan (25), maternal serum 25OHD levels are not related to the risk of obstructed labor. Maternal serum 25OHD levels are higher (37%) in the nulliparous obstructed labor cases than the nulliparous controls (not age-matched); otherwise, their nutritional status is similar. In contrast, a case-control study in Boston finds 32% lower maternal serum 25OHD levels in C-section cases compared with vaginally delivered controls, and an increased risk of C-section (OR = 3.84) with low serum 25OHD levels <37.5 nmol/L (91).

GDM in relation to maternal vitamin D status is examined in four observational studies (31, 41, 80, 112), which report contradictory results. Maternal serum 25OHD levels are low in a cohort study in Southern India but are not associated with GDM (41), whereas in a cross-sectional study, maternal serum 25OHD levels are 23% and 18% lower in those with GDM or impaired glucose tolerance, respectively, than in those with normal glucose tolerance (80). Prevalence of severely low levels <12.5 nmol/L is higher in those with GDM (44%) than in those with normal GT (24%). In a prospective study, maternal serum 25(OH)D levels, although 11% lower in those with GDM, do not alter the risk of GDM (31). Finally, those homozygous for the "AA" CYP27B1(260) allele have higher maternal serum 25OHD levels compared to those either homozygous or heterozygous for the "C" allele (111). Only 30% of GDM patients with serum 25OHD levels <50 nmol/L have an "A" allele compared with 42% with levels >50 nmol/L. Thus, genetic variation may influence circulating levels of serum 25OHD levels. The extent to which such variation contributes to the contradictory results in observational studies on the risk for GDM and, possibly, other health outcomes is unknown but is important to determine.

Infectious disease in relation to maternal vitamin D status is examined in four observational studies focused on bacterial vaginosis (one prospective cohort and one cross-sectional study), periodontal disease (one case-control study), and maternal HIV transmission (one cohort study). Consistently, lower maternal 25OHD levels mid-gestation are associated with increased risk of bacterial vaginosis [OR = 2.87 with <75 nmol/L (59); OR = 1.26 with ≤50 nmol/L and 1.65 ≤20 nmol/L (17)], severe periodontal disease (OR = 2.2; 19), and HIV transmission or death at birth in HIV-infected pregnant women in Tanzania (49%; 90). Infectious disease is the only maternal adverse outcome for which the observational findings consistently show increased risk at lower maternal serum 25OHD levels. Assessment of maternal prepregnancy vitamin D status, rather than mid-gestational status, is needed in light of the potential role of placental anti-infective factors including cathelicidin (an antimicrobial peptide) shown to be regulated by $1,25(OH)_2D$ in placental

trophoblasts in vitro (79). A high priority is research to assess whether vitamin D plays a causal role in preventing maternal infections.

Summary. The evidence for all nonbone health outcomes, except for infectious diseases, is contradictory, lacks causal inference, and is thus inconclusive. Rigorous placebo-controlled RCTs are needed that examine physiologically relevant intakes of supplemental vitamin D prior to pregnancy through postpartum while ensuring that dietary calcium intakes and phosphorous are appropriate to meet the DRIs and that confounders such as season and latitude (i.e., ultraviolet B exposure), BMI, and cultural factors that affect endogenous synthesis of vitamin D are controlled. In addition, studies need to determine the gene-nutrient interactions possible through polymorphisms in key genes in vitamin D metabolism, such as 1-α-hydroxylase, 24-hydroxylase, and DBP. Only such studies can elucidate any causal effect of maternal vitamin D status on the risk of PE, obstructed labor and C-section, GDM, and infectious disease and can determine whether genetic polymorphisms enhance or ameliorate this risk.

Fetal adverse outcomes beyond bone health. Birthweight is reported relative to maternal vitamin D status in 4 RCTs and 11 observational studies. Vitamin D supplementation ranging from 800 to 1,000 IU/day or a single large dose of 200,000 IU in the last trimester does not affect birthweight in three RCTs (24, 83, 142), only one of which is placebo controlled (24). Nor is a relationship with maternal serum 25OHD levels found in six observational studies (1, 32, 41, 45, 95, 109). In contrast, supplemental vitamin D (1,200 IU/day with 375 mg Ca/day or a single large dose of 600,000 IU in the last trimester) in Indian women increases birthweight 6% and 12%, respectively, in a nonplacebo-controlled RCT (86). Furthermore, an inverse relationship of maternal 25OHD with birthweight is reported in four observational studies (75, 89, 119, 137). Birthweight Z score inversely correlates with maternal postpartum 25OHD level (137). Interestingly, in a subsequent subanalysis from their original study, in which no relationship is seen (95), Morley and colleagues (96) report a VDR *Fok* modifier effect such that maternal vitamin D deficiency, defined as <28 nmol/L, is associated with 8% lower birthweight in *Vdr* FF/Ff genotype ($p < 0.02$).

Small for gestational age (SGA) is reported relative to maternal vitamin D status in one RCT and two observational studies. Supplemental vitamin D (800 IU/day or a single large dose of 200,000 in the last trimester) does not affect the incidence of SGA (142), although the researchers note that maternal serum 25OHD levels >50 nmol/L are achieved only in 30% of the supplemented women even though maternal 25OHD levels increase 41% with supplementation. Maternal serum 25OHD levels <29.9 nmol/L, but not those ≥30 to <50 nmol/L, are associated with an increased adjusted risk of 90% for SGA in a prospective cohort study (75). However, a U-shaped risk relationship for SGA is observed in white, but not black, women in another prospective cohort study (16), with increased risk associated with <70 nmol/L serum 25OHD levels (OR = 2.7) and >70 nmol/L (OR = 3.9). Thus, the relationship of maternal vitamin D status and SGA is inconclusive in light of the negative RCT and inconsistent findings from the observational studies in which increased risk is reported at maternal serum 25OHD levels <29.9 nmol/L and >70 nmol/L in white women, but not between 30 to 50 nmol/L. RCTs with physiologically relevant doses are needed to assess the role of maternal vitamin D status and SGA.

Gestational duration is reported with conflicting results in two observational studies. A decrease of 0.7 weeks duration is associated with low maternal serum 25OHD levels <29.9 nmol/L (95), but no effect on gestational duration is reported with low total dietary vitamin D intakes (<200 IU/day) (119).

Summary. The evidence associating maternal vitamin D status to fetal nonbone health

outcomes is inconsistent and lacks causality. Relatively few of these observational studies on nonbone health fetal outcomes consider confounding factors such as maternal prepregnant BMI, race/ethnicity, or maternal nutritional status. With only a few exceptions (86, 109) dietary calcium intake is not considered, and dietary phosphorous intake is not considered. Other potential risk factors known to affect fetal growth and SGA, such as socioeconomic status, unintended pregnancy, and maternal weight gain, are also typically not considered in the analyses.

Developmental programming of health outcomes in later life. Interest in exposure in utero to maternal vitamin D on health outcomes in later life, termed developmental programming, has grown to include bone health, type 1 diabetes (T1Db), and inflammatory and immune disorders such as asthma, wheezing, and food allergies. Research also is reported on infant supplementation and later health outcomes (PE, T1Db) but is not discussed here because it exceeds the focus of this review. The discussion below addresses those studies in which maternal/fetal vitamin D status is assessed using dietary intake or serum 25OHD levels. Examining developmental programming in humans presents challenges, and potential confounders typically are not well considered, including other nutritional factors and status (especially calcium or phosphorous), except in a few studies (43, 68, 84, 99, 137); maternal weight gain; maternal prepregnant BMI; and socioeconomic status, except in a few studies (45, 68, 137). Furthermore, the influence of some of these confounders could extend beyond the prenatal to the postnatal period (66).

Bone health. Two longitudinal cohort studies report an inverse relationship of maternal serum 25OHD levels at term with offspring's skeletal health (68, 136). Follow-up was reasonable in both studies (59% to 70%). Children born to mothers with serum 25OHD levels <27.5 nmol/L have lower total and lumbar BMC (DEXA) at nine years in comparison with those born to mothers with levels >50 nmol/L (68). Children born to mothers with serum 25OHD levels <42.6 nmol/L sustain lower tibia cross-sectional area from birth through 14 months but restore tibia BMC to levels comparable to children born to mothers with higher serum 25OHD levels (136). Calcium (820 to 840 mg/day) and vitamin D (488 to 496 IU/day) intakes are appropriate for age in both studies. Whether these reductions in skeletal parameters will be sustained remains to be determined.

Type 1 diabetes. T1Db diabetes risk is assessed relative to maternal vitamin D intake in two longitudinal cohort studies (43, 84), which purportedly report conflicting results. Maternal vitamin D intake only from food, not supplements [assessed by Food Frequency Questionnaire (FFQ) in the third trimester], is positively associated with the risk for islet autoimmunity by age 4 years but only approached statistical significance (Wald χ^2; $p = 0.059$; 43). Total vitamin D intake is not assessed. Maternal vitamin D intake from food or supplements or both (assessed by retrospective FFQ one to three months postpartum) is not associated with beta cell autoimmunity/T1Db up to age 9 years (84). Consideration of maternal serum 25OHD levels would have strengthened both studies. Neither study supports developmental programming of T1Db by maternal vitamin D intake during pregnancy, but each has major limitations, with retrospective FFQ in one and a failure to analyze total vitamin D intake in the other.

Inflammatory and immune disorders. Asthma and wheezing risk at ages from 2 to 5 years is consistently inversely associated in four prospective longitudinal birth cohort studies with either cord blood 25OHD levels (27) or vitamin D intakes (37, 40, 92). In one study, maternal dietary intake is assessed with retrospective FFQ for the eighth month of pregnancy, a serious limitation of the study (40). Maternal vitamin D intake is associated at age 5 years with allergic rhinitis (OR = 0.85; 40) and with allergic sensitization to

specific food allergens (by IgE determination; OR = 0.56; 99), again with retrospective FFQ. Of note, however, is that maternal serum 25OHD levels >75 nmol/L are associated with increased risk of eczema (OR = 5.4) in comparison with levels <30 nmol/L (45). Overall, a consistent association of low maternal vitamin D status is only seen for inflammatory and immune-related disorders (asthma, wheezing, and allergies). Furthermore, a suggestion is emerging of risk for eczema at both low and high maternal vitamin D status.

VITAMIN D AND LACTATION

Physiology of Vitamin D in Lactation

Multiple issues concern the physiology of vitamin D in lactation: physiologic changes in the mother, vitamin D content in the milk and its relationship to maternal vitamin D status, and the resulting nutritional status of the infant. In addition, to understand how maternal vitamin D seems to play little role in maternal calcium homeostasis during lactation (66), it is important to understand how the calcium in human breast milk (HBM) is provided. Considerable evidence (for a recent review, see 66) demonstrates that key physiologic changes in the mother result in a transient mobilization of calcium from her bones. Indeed, a clinical trial finds no effect of maternal supplementation with 1,200 IU/day of vitamin D_2 for four weeks on HBM calcium (129), nor are maternal serum 25OHD levels and HBM calcium content related in Gambian or British women at three months of lactation (111). Discussed below are changes in vitamin D metabolites in lactation and HBM content of vitamin D and its metabolites.

Vitamin D and metabolites. Maternal serum vitamin D and metabolite levels are reported in two longitudinal studies (64, 140) and one cross-sectional study (71). Serum 25OHD levels, but not free 25OHD, decrease approximately 31% from birth through the first 4 weeks of lactation and then are sustained at a lower level through 21 weeks (64). Serum total and free $1,25(OH)_2D$ levels also decrease sharply within two weeks after birth (140), by approximately 60% in the first 4 weeks (64), and are relatively stable through 12 weeks lactation, and then increases slightly by 18 (140) to 21 weeks (64) of lactation. DBP also decreases sharply at birth, approximately 25% by 4 weeks lactation, and remains lower through 18 weeks (140). Serum 5OHD and $1,25(OH)_2D$ levels are similar, however, in women lactating and in those weaning their infants (71), but serum $1,25(OH)_2D$ levels are higher in women weaning their infants than in nonlactating control women. Serum PTH levels are also similar in lactating and weaning women.

Vitamin D and its metabolites in human milk. The content of vitamin D and its metabolites in HBM are reported in five studies measured by competitive binding protein assay at 1 to 30 days postpartum (28, 62), 0.5 to 4 months postpartum (61, 101), or an unspecified time postpartum (127); two studies by high-performance liquid chromatography at 8 to 20 weeks postpartum (2, 129); and one study by liquid chromatography-tandem mass spectrometry at 3 to 268 days postpartum (72). Three of the studies (2, 127, 129) use milk samples collected from the first morning feeding with total milk (129), combined fore-, mid-, and hindmilk (127), or fore- and hindmilk samples (2), whereas one uses foremilk only from random times (101), one uses midmilk from an unspecified times (72), one uses unspecified sampling at random times (28), and two use an unspecified sampling strategy (61, 62). Reports conflict on whey versus whole milk content, with one finding higher vitamin D and its metabolite levels in whey (62) and the other finding little detectable in whey (2). In this latter study, hind milk (rich in fat) is higher in content (49%) than is foremilk (lower in fat), consistent with their analytical findings of little content in separated whey. Vitamin D content ranges from 39 pg/ml (62) to 579pg/ml (127) and is low compared with maternal serum levels (17.8%; 61). 25OHD content ranges from 84 pg/ml

(72) to 1,900 pg/ml (101) and is proportionately lower—compared to maternal serum 25OHD levels (0.9%; 61)—than the ratio of HBM to maternal vitamin D levels. $1,25(OH)_2D$ ranges from 5.1 pg/ml (62) to 22 pg/ml (129). Vitamin D and $25OHD_3$ content does not vary from colostrum to transitional to mature milk, whereas $25OHD_2$ decreases 50% from colostrum to transitional milk and remains low in mature milk (72). HBM vitamin D and 25OHD levels are lower in African Americans (33% for 25OHD and 68% for vitamin D; 122). DBP is also present in HBM at 3.3% the level found in maternal serum and is unrelated to the vitamin D or 25OHD content (61), but its source is not clear. Thus, HBM contains little total vitamin D activity: The average across studies is 544 pg/ml, which would provide approximately 15 IU/day to the exclusively breastfed infant in the first six months.

The effect of maternal status and supplemental vitamin D on HBM content varies among studies. HBM vitamin D levels correlate with maternal serum vitamin D levels [$r^2 = 0.33$ (127); $r^2 = 0.48$ (61)]. Conflicting results are reported on the correlation of HBM 25OHD with maternal serum 25OHD levels, with no correlation in two studies (28, 127) and a positive correlation in two studies [$r^2 = 0.14$ to 0.18 (61); $r^2 = 0.38$ (64)]. Levels of vitamin D and 25OHD in HBM do not correlate (72). Seasonal variation in content is also noted by Ala-Houhala and colleagues (2).

Maternal supplemental vitamin D (1,000 to 2,000 IU/day) increases HBM 25OHD 199%, but not vitamin D (2). Supplementation with 1,200 IU/day of vitamin D_2 for four weeks increases HBM vitamin D 93% (as vitamin D_2) and $24,25(OH)_2D$ 19%, but does not affect total 25OHD or $1,25(OH)_2D$ levels (129). Maternal supplementation with 1,600 or 3,600 IU/day of vitamin D_2 and 400 IU/day of vitamin D_3 (total 2,000 and 4,000 IU/day) also increases HBM vitamin D and metabolites (reported as a summed total antirachitic activity in IU) approximately 200% and 400%, respectively, after three months (63), as does a higher dose of 6,400 IU/day (6,000 IU D_2 and 400 IU D_2; 138) with approximately 1,000% increase after one month and 2,300% after six months. Unfortunately, the chemical form of vitamin D most contributing to these large increases in HBM with high-dose maternal supplementation cannot be identified because, although measured, the chemical forms are not reported. Only one study does not find an increase in HBM vitamin D content with 983 IU/day of vitamin D in cod liver oil supplement (101). Taken together, the evidence strongly supports an increased response of HBM vitamin D and 25OHD content to maternal vitamin D supplementation from 1,000 IU to 6,400 IU/day.

Why such small amounts of maternal vitamin D and its metabolites are transferred across the lactating mammary epithelium to breast milk is unknown. What role, if any, either maternal or HBM DBP play in this transfer is unclear. Understanding the mechanism of transfer might enable more effective strategies to increase milk total vitamin D activity without excessive exposure of the mother to very high intakes of vitamin D.

Infant serum vitamin D and metabolite levels are reported by four longitudinal studies (29, 48, 64, 85), one RCT (115), and two cohort studies (77, 127). Serum total (48, 64, 85, 115) and free levels (64) of 25OHD decrease ranging from 41% to 87% in the first six to eight weeks of exclusive breast-feeding and 25% over six months of breast-feeding (48). Similarly, serum total (64, 85) and free (64) $1,25(OH)_2D$ levels also decrease up to 75% during this initial period, but increase 16% to 30% by 6 to 12 months (48). Serum PTH levels also decrease approximately 25% over 12 months (48). Conflicting results are reported on differences between European American and African American exclusively breastfed infants: 30% lower serum 25OHD levels in African American infants are reported after an unspecified period in one study (127), but no difference at six months in another study (77). However, serum 1,25(OH)2D levels are 19% lower in African American infants in the latter study. Season affects serum 25OHD levels and serum $1,25(OH)_2D$ levels in both European

American and African American infants, with higher 25OHD levels in summer and lower $1,25(OH)_2D$ levels in winter (77). Results conflict on the correlation of infant serum 25OHD levels with maternal serum 25OHD levels in exclusively breast-fed infants: A positive correlation is reported at four days and six weeks ($r^2 = 0.25$ and 0.33, respectively) in one study (115), but no correlation is reported in another study (127). Serum DBP does not differ between the two groups of infants (77). Consistently, infant serum total and free 25OHD and $1,25(OH)_2D$ levels decrease early in exclusive breast-feeding and remain low through the first 12 weeks of breast-feeding.

Effect of maternal status and supplementation on infant serum 25OHD levels and other metabolites is reported in three RCTs in exclusively breast-fed infants, with differing results. Maternal supplementation with 2,000 IU/day, but not 1,000 IU/day, for 15 weeks achieves infant serum 25OHD levels and $1,25(OH)_2D$ levels comparable to those achieved by infant supplementation with 400 IU/day (approximately 71 to 80 nmol/L; 3). In a double-blind RCT without a placebo or infant supplemented control group, maternal supplementation for three months increases infant serum 25OHD levels 356% and 230%, respectively, to levels >50 nmol/L (7). Comparable serum 25OHD levels are achieved (approximately 112 nmol/L) with maternal supplementation of 6,400 IU/day and infant supplementation of 300 IU/day (138), but infant levels achieved with the 400 IU/day maternal supplementation (control), unfortunately, are not reported. Others report serum 25OHD levels from 58 (29) to 100 nmol/L (48) with 400 IU/day of infant supplementation for six months. Consistently, infant serum calcium and phosphate levels are comparable across all groups (3, 138), as are all growth parameters (138).

Maternal and Infant Health Outcomes

Maternal bone health. Loss of maternal bone mineral during lactation and its restoration postweaning is well established (reviewed in 66) and seems largely unrelated to maternal vitamin D status. Loss of 6% lumbar spine BMD occurs even while serum 25OHD levels increase 45% postweaning (35) and serum $1,25(OH)_2D$ levels are unchanged. Serum 25OHD, $1,25(OH)_2D$, and PTH do not correlate with femoral and lumbar BMD and decrease similarly in women who are breast-feeding, partially breast-feeding, and formula-feeding (125). No RCT examining the effect of maternal supplemental vitamin D on the bone health of mothers during lactation could be identified. In the long term, lactation is protective against osteoporosis (66). Recent studies exemplify this evidence (117, 118), with an OR of 0.38 reported (118).

Infant bone health. Although exclusively breast-fed infants not receiving supplementation have reduced, and in some cases low, serum 25OHD levels (115), signs of rickets are generally not found in the first six months (115). The AHRQ evidence-based review could not identify a threshold for serum 25OHD levels (33), but the IOM DRI committee noted an increased risk of rickets below 30 nmol/L (66). BMC (by DEXA) is similar in exclusively breast-fed infants supplemented or not with 400 IU/day of vitamin D (29) and in breast-fed and formula-fed infants (even though breast-fed infants have 45% lower serum 25OHD levels; 103). The impact on bone health of lower serum 25OHD levels in exclusively breast-fed infants seems on average minimal in the first six months.

Other health outcomes. The growth of exclusively breast-fed infants is unaffected by either infant (400 IU/day; 29) or maternal (additional 6,000 IU/d; 138) supplemental vitamin D. One retrospective case series (82) reports 16 cases of exclusively breast-fed infants of Indian or African ethnicity with clinical heart failure (severe cardiomyopathy or cardiac arrest) in whom serum 25OHD levels are very low (mean 18.5 nmol/L), PTH levels are high (mean 34 pmol/L), and total calcium is very low (1.5 mmol/L). In a case study, an increased risk of urinary tract infections in exclusively

breast-fed infants supplemented with vitamin D is reported (73), but as noted by Linday and colleagues (78), this study is limited by the use of risk analysis designed for population analysis instead of a statistical approach more appropriate for the analysis of samples, inclusion of mixed-fed infants, concerns about the case incidence, and lack of consideration of the amount and type of supplementation. Thus, very low vitamin D levels in exclusively breast fed infants are associated with hypocalcemia and clinical cardiac failure in at-risk ethnic infants.

DIETARY RECOMMENDATIONS AND STATUS

2011 Dietary Reference Intakes

The 2011 DRIs for vitamin D are based on bone health, the only health outcome of the 24 evaluated for which sufficient evidence of cause and effect and dose response data needed for specifying the DRIs could be identified (66). In adults (using an integrated bone health indicator with calcium absorption and osteomalacia for bone maintenance) and in adolescents (using an integrated bone health indicator with calcium absorption, rickets, and BMC/BMD for bone accretion), serum 25OHD levels ≥50 nmol/L meet the needs of 97.5% of healthy adults and adolescents, a level consistent with an RDA. Serum 25OHD levels of 40 nmol/L meet the needs of 50% of healthy adults and adolescents, a level consistent with the IOM's Estimated Average Requirement (EAR). The RDA and EAR were specified assuming minimal sun exposure because of the lack of evidence for dose response from sun exposure and for the known risk of UV radiation and skin cancer. Establishing DRIs for vitamin D assuming minimal exposure also addresses the variability in endogenous production due to geographic latitude, season, skin pigmentation, and cultural and behavioral factors. A simulated dose-response of achieved serum 25OHD levels versus total dietary vitamin D intake from foods and supplements was done by regression analysis of achieved serum 25OHD levels versus the natural logarithm of total dietary vitamin D intake, (the best curvilinear fit) based on RCTs conducted in the winter at latitudes >50° or in Antarctica. Of note, the simulated dose response was not affected by age from 5 to over 70 years. No dose-response studies meeting the inclusion criteria were identified in pregnant or lactating women. From this simulated dose response, the EAR for adolescents and adults was set at 400 IU/day and the RDA was set at 600 IU/day.

EAR and RDA for pregnancy and lactation. The EAR and RDA for both pregnancy and lactation are also set at 400 IU/day and 600 IU/day, respectively, based on the evidence that needs do not increase in pregnancy or lactation (66). For pregnancy, this evidence includes the insufficiency of evidence on the association of serum 25OHD levels and maternal BMD found by the AHRQ systematic evidence-based review (33); no effect of maternal 25OHD level on fetal calcium homeostasis or skeletal outcomes based on one RCT (36); and no effect on fetal calcium homeostasis or skeletal outcomes of the genetic absence of VDR or 1-α-hydroxylase. For lactation, this evidence includes no effect of maternal status on breast milk calcium content (111) or serum 25OHD levels in the breast-fed infant based on RCTs and observational studies (reviewed above and in the IOM report; 66), except at very high intakes (>4,000–6,400 IU/day) (138). These very high intakes are at or above the tolerable upper intake level (UL) discussed next. Furthermore, an Adequate Intake[4] of 400 IU/day for infants (an intake consistent with the recommendations of the American Academy of Pediatrics) is set to ensure serum 25OHD levels consistent with bone health (66).

Upper intake level. The tolerable upper level is the level of daily intake over an extended period above which the risk of adverse effects

[4]An Adequate Intake, set when insufficient evidence is available to specify an EAR, is intended to meet or exceed the needs of most persons in the life-stage group (66).

increases. For adults, the UL was set on the basis of evidence from hypercalcemia in acute vitamin D toxicity at 10,000 IU/day. Evidence from two RCTs (7, 138), in fact, does not find maternal hypercalcemia with supplemental vitamin D from 4,000 to 6,400 IU/day. This level, associated with acute toxicity and hypercalcemia, was adjusted for the uncertainty arising from emerging evidence of increased risk (from U-shaped relationships at both low and high serum 25OHD levels) at higher levels of 25OHD (125–150 nmol/L) for all-cause mortality, certain cancers (pancreatic, prostate, and breast), cardiovascular disease, and fractures. The UL is, thus, set at 4,000 IU/day, a level resulting in 25OHD levels of approximately 150 nmol/L (57). Because no data for pregnant and lactating women provided a different basis for establishing another UL specific to these life stages, the UL for pregnant women and adolescents and for lactating women and adolescents is also set at 4,000 IU/day. Worth noting, however, are two recent studies: one by Bodnar and colleagues (16) in which a U-shaped relationship of risk for SGA and serum 25OHD levels is observed in white women with increased risk at levels >70nmol/L, and the second by Gale and colleagues (45), in which risk of eczema at age 5 years increases with maternal serum 25OHD levels >75 nmol/L, mirroring the emerging concerns for other health outcomes in adults. For both SGA and eczema, the increased risk at higher levels occurs at 25OHD levels similar to those considered by the IOM DRI committee in establishing the UL at 4,000 IU/day. Immediate and long-term effects of high serum 25OHD levels in lactating women have not been well studied, but for the protection of public health, the caution of avoiding high maternal serum 25OHD levels is warranted.

Vitamin D Status of Pregnant and Lactating Women in the United States

Assessing the vitamin D status of pregnant and lactating women presents the same challenges that have been described in other life stages (66). Relative contributions from endogenously produced vitamin D are difficult to determine given the paucity of data on the dose response from sun exposure and the many biobehavioral factors that influence sun exposure, including season, latitude, cloud cover, pollution, skin pigmentation, use of sun protection, and ethnic, religious, and cultural dress practices of covering exposed skin (especially for reproductive-aged women). The inherent limitations of FFQs and dietary recall methods and the limitations of food composition databases for vitamin D are also challenges, although improved methods of assessing vitamin D in foods have been developed, and the USDA Food Composition Database has been updated (66). Furthermore, obesity reduces serum 25OHD levels (66). The impact of these challenges is well reflected in the most recent data from the U.S. National Health and Nutrition Examination Survey (NHANES) (66) across males and females from 1 to 70+ years of age. Total dietary intake from food and supplements (323 $\pm$ 62 IU/day) is less than the EAR (400 IU), but serum 25OHD levels (adjusted appropriately for assay drifts/shifts), which reflect total exposure from diet and endogenous sources, are 58.9 $\pm$ 14.0 nmol/L, well above the 40 nmol/L linked to the EAR and even above the 50 nmol/L linked to the RDA of 600 IU/day. Most likely, incidental sun exposure contributions account for the discrepancy. On the basis of DRI simulated dose-response analyses (66), it appears that some incidental sun exposure contributes to vitamin D status: 24% greater 25(OH)D is achieved at northern latitudes in the United States and Canada (41° to 48°N) in comparison with levels at more northern latitudes (>50°N), per unit of total vitamin D intake. For these reasons, maternal serum 25OHD levels are the best indicator of total exposure of pregnant and lactating women to vitamin D from all sources.

Another challenge is interpreting maternal serum 25OHD levels in the absence of evidence-based consensus guidelines, as noted by the IOM DRI committee (66), particularly because no health outcomes are validated relative to serum 25OHD levels in either pregnant

or lactating women, and serum 25OHD levels change during lactation. Risk of rickets or osteomalacia increases below serum 25OHD levels of 30 nmol/L across life-stage groups (66), but an individual with such low levels does not necessarily have frank vitamin D deficiency. Consistent with the interpretation of the EAR and RDA, serum 25OHD levels <40 suggest an increased risk for inadequate intake, and levels ≥50 nmol/L suggest that most needs have been met. However, a wide array of cut-off values for deficiency (<10 to <80 nmol/L), insufficiency (<50 to <75), and sufficiency (≥50 to ≥75 nmol/L) are used throughout the literature.

Vitamin D Status of pregnant women in the United States. The most current data from the nationally representative U.S. NHANES for pregnant women have been analyzed recently (47). However, the results of this study are weakened by its failure to analyze usual intakes and by its failure to address the documented and serious assay drifts and shifts in the NHANES serum 25OHD analysis. Thus, the validity of the results and conclusions concerning vitamin D status from dietary intake and serum 25OHD levels are uncertain in the absence of knowing how adjusting for the assay shifts and drifts would affect the distribution of serum 25OHD. What is informative from this study is the use of supplemental vitamin D in pregnant women in the United States. Only 28% do not use a vitamin D supplement, markedly lower than the 68% of nonpregnant women who do not use a vitamin D supplement. Of pregnant supplement users, 7% take 1 to 399 IU/day, and 66% take >400 IU/day of supplemental vitamin D; 29% take supplements for >181 days, and 21% do so for 31 to 181 days of pregnancy (47). A rigorous and appropriate analysis of current NHANES data for pregnant women is needed to determine the vitamin D status on the basis of total usual dietary intake and serum 25OHD levels adjusted for the assay drifts/shifts.

Four recent cohort studies in pregnant adults and one in adolescents provide some information on vitamin D status, although none is nationally representative. Overall, 41% of the pregnant women (mean age 25 to 30 years) have serum 25OHD levels <50 nmol/L, with more African Americans (approximately 78%) below this level than Hispanic Americans (approximately 33%) and European Americans (approximately 13%; 69). From a series of three studies from two cohorts (13, 15, 18), 5% and 29% of pregnant European Americans and African Americans, respectively, have serum 25OHD levels <37.5 nmol/L (15). The cut-point for insufficiency (38 to 80 nmol/L) that is used unfortunately does not allow determination of the prevalence of serum 25OHD levels <50 nmol/L. Seasonal variation in winter compared with summer (after adjustment for BMI and periconceptional vitamin use by 90%) is 42% lower in African American women than European American women. Pregnant women obese prior to pregnancy have a higher prevalence (40% to 61%) of serum 25OHD levels <50 nmol/L than do women overweight prior to pregnancy (33% to 48%) or women with normal weight prior to pregnancy (26% to 36%; 13). In a cohort study in Baltimore (100), prevalence of serum 25OHD levels <37.5 nmol/L and <50 nmol/L in pregnant African American adolescents are 7% to 30% (summer and winter, respectively) and 30% to 56% (summer and winter, respectively).

Overall, the prevalence of low vitamin D levels indicative of inadequacy based on the EAR-linked value of <40 appears to be low in pregnant European Americans even in the northern United States (5%), higher in African Americans (29%), and similar in adolescents (7%). The studies, however, used a slightly lower serum 25OHD level (<37.5 nmol/L) to determine prevalence. Furthermore, many pregnant women in the United States are meeting their needs for vitamin D, as indicated by the prevalence of serum 25OHD levels >50 nmol/L in 40% to 74%, although the prevalence of meeting their needs is lower in African American and obese women and during the winter. Still, vitamin D is a nutrient of concern for American pregnant women and

adolescents, particularly for African Americans and obese individuals.

Vitamin D status of lactating women in the United States. Less is known about the vitamin D status of lactating women. No nationally representative analysis has been reported. In part, this absence may reflect the small number of lactating women in the NHANES data set (only 101 for 2003–2006). Nonetheless, inclusion of the assessment of maternal and infant serum 25OHD levels in early (2 to 4 weeks) and mid (12 to 16 weeks) lactation in a nationally representative study, such as the National Children's Study, would greatly enhance our understanding of the prevalence of inadequacy in lactating women in the United States. None of the cross-sectional, RCT, or longitudinal studies in the past ten years are informative because only mean serum 25OHD levels are reported or because inappropriately high cut-points are used to assess prevalence of deficiency or insufficiency.

KNOWLEDGE GAPS AND RESEARCH NEEDS

The mechanisms whereby physiologic changes occur in maternal vitamin D metabolism during pregnancy are unknown. Specifically, research is needed to determine how maternal DBP and serum $1,25(OH)_2D$ levels increase as well as the role of the kidney and placenta in this increase. For all maternal and fetal bone and nonbone health outcomes, rigorous randomized clinical trials are needed to determine the role of maternal vitamin D and status on these outcomes. High priority should be given to maternal infectious disease, for which consistent observational associations exist. Finally, research is needed to understand genetic variants in the vitamin D metabolic pathway, particularly in *Vdr*, *Cyp27B1*, and *Cyp2R1*, relative to their impact on risk to the maternal and fetal outcomes and interaction with maternal vitamin D status

Research is also needed to elucidate the mechanism of transfer of vitamin D and its metabolites across the lactating mammary epithelium and the consequence of high maternal supplementation to long-term maternal health outcomes and infant bone and nonbone health outcomes. Assessment of vitamin D status in a nationally representative sample of American lactating women is also needed to inform public health policy and guidelines.

SUMMARY AND CONCLUSIONS

Key physiologic changes occur during pregnancy and lactation in maternal calcium homeostasis that are independent of vitamin D. The role of vitamin D on maternal and fetal bone health outcomes is not fully understood. The relationship of maternal vitamin D and maternal adverse outcomes including preeclampsia, gestational diabetes, obstructed labor, and C-section is not clear. Only for maternal infections is the observational evidence consistent in associating increased risk of infection with low maternal vitamin D status. Overall, the evidence lacks causality, as no double-blinded placebo-controlled RCTs have been conducted on nonbone health outcomes. The evidence on vitamin D on fetal adverse outcomes is also contradictory and lacking in causality for growth and developmental programming of subsequent bone health, T1Db, and inflammatory and immune-related disorders.

The 2011 DRIs for vitamin D were set on the basis of an integrated bone health indicator and a simulated dose-response assuming minimal sun exposure. The EAR is 400 IU/day, and the RDA is 600 IU/day for pregnant and lactating women and adolescents. The 4,000 IU/day UL is based on hypercalcemia resulting from acute toxicity adjusted for the uncertainty arising from emerging evidence of U-shaped risk relationships for all-cause mortality, certain cancers, cardiovascular disease, and fracture risk. Increased risk for these is associated with serum 25OHD levels greater than 150 nmol/L. Recent evidence associates increased risk of SGA with maternal serum 25OHD levels above 70 nmol/L. Prevalence of inadequacy in American pregnant women

ranges from 5% to 29%, but concerning limitations exist in the evidence. Little is known about the vitamin D adequacy in American lactating women.

Research is needed to understand the metabolic alterations for vitamin D during pregnancy, the mechanism of its transfer across the lactating mammary epithelium, the status of American pregnant and lactating women, and the relationship of genetic polymorphisms in *Vdr* and *Cyp27B1* with vitamin D status and maternal and fetal outcomes. Especially needed are rigorous and well-designed RCTs to determine the relationship of vitamin D status with maternal and fetal bone and nonbone health outcomes.

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LITERATURE CITED

1. Akcakus M, Koklu E, Budak N, Kula M, Kurtoglu S, Koklu S. 2006. The relationship between birth weight, 25-hydroxyvitamin D concentrations and bone mineral status in neonates. *Ann. Trop. Paediatr.* 26(4):267–75
2. Ala-Houhala M, Koskinen T, Parviainen MT, Visakorpi JK. 1988. 25-Hydroxyvitamin D and vitamin D in human milk: effects of supplementation and season. *Am. J. Clin. Nutr.* 48(4):1057–60
3. Ala-Houhala M, Koskinen T, Terho A, Koivula T, Visakorpi J. 1986. Maternal compared with infant vitamin D supplementation. *Arch. Dis. Child.* 61(12):1159–63
4. August P, Marcaccio B, Gertner JM, Druzin ML, Resnick LM, Laragh JH. 1992. Abnormal 1,25-dihydroxyvitamin D metabolism in preeclampsia. *Am. J. Obstet. Gynecol.* 166(4):1295–99
5. Baker AM, Haeri S, Camargo CA Jr, Espinola JA, Stuebe AM. 2010. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. *J. Clin. Endocrinol. Metab.* 95(11):5105–9
6. Barragry JM, Corless D, Auton J, Carter ND, Long RG, et al. 1978. Plasma vitamin D-binding globulin in vitamin D deficiency, pregnancy and chronic liver disease. *Clin. Chim. Acta* 87(3):359–65
7. Basile LA, Taylor SN, Wagner CL, Horst RL, Hollis BW. 2006. The effect of high-dose vitamin D supplementation on serum vitamin D levels and milk calcium concentration in lactating women and their infants. *Breastfeed. Med.* 1(1):27–35
8. Beck-Nielsen SS, Brock-Jacobsen B, Gram J, Brixen K, Jensen TK. 2009. Incidence and prevalence of nutritional and hereditary rickets in southern Denmark. *Eur. J. Endocrinol.* 160(3):491–97
9. Begum R, Coutinho ML, Dormandy TL, Yudkin S. 1968. Maternal malabsorption presenting as congenital rickets. *Lancet* 1(7551):1048–52
10. Bikle DD, Gee E, Halloran B, Haddad JG. 1984. Free 1,25-dihydroxyvitamin D levels in serum from normal subjects, pregnant subjects, and subjects with liver disease. *Endocrinology* 115(6):2077–84
11. Bikle DD, Halloran BP, Harris ST, Portale AA. 1992. Progestin antagonism of estrogen stimulated 1,25-dihydroxyvitamin D levels. *J. Clin. Endocrinol. Metab.* 75(2):519–23
12. Black AJ, Topping J, Durham B, Farquharson RG, Fraser WD. 2000. A detailed assessment of alterations in bone turnover, calcium homeostasis, and bone density in normal pregnancy. *J. Bone Miner. Res.* 15(3):557–63

13. Bodnar LM, Catov JM, Roberts JM, Simhan HN. 2007. Prepregnancy obesity predicts poor vitamin D status in mothers and their neonates. *J. Nutr.* 37(11):2437–42
14. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. 2007. Maternal vitamin D deficiency increases the risk of preeclampsia. *J. Clin. Endocrinol. Metab.* 92(9):3517–22
15. Bodnar LM, Catov JM, Wisner KL, Klebanoff MA. 2008. Racial and seasonal differences in 25-hydroxyvitamin D detected in maternal sera frozen for over 40 years. *Br. J. Nutr.* 101(2):278–84
16. Bodnar LM, Catov JM, Zmuda JM, Cooper ME, Parrott MS, et al. 2010. Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women. *J. Nutr.* 140(5):999–1006
17. Bodnar LM, Krohn MA, Simhan HN. Maternal vitamin D deficiency is associated with bacterial vaginosis in the first trimester of pregnancy. *J. Nutr.* 139(6):1157–61
18. Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM. 2007. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. *J. Nutr.* 137(2):447–52
19. Boggess KA, Espinola JA, Moss K, Beck J, Offenbacher S, Camargo CA. 2011. Vitamin D status and periodontal disease among pregnant women. *J. Periodontol.* 28(3):247–52
20. Bouillon R, Van Assche FA, Van Baelen H, Heyns W, De Moor P. 1981. Influence of the vitamin D-binding protein on the serum concentration of 1,25-dihydroxyvitamin D3. Significance of the free 1,25-dihydroxyvitamin D3 concentration. *J. Clin. Invest.* 67(3):589–96
21. Bouillon R, Verstuyf A, Mathieu C, Van Cromphaut S, Masuyama R, Dehaes P. 2006.Vitamin D resistance. *Best Pract. Res. Clin. Endocrinol. Metab.* 20(4):627–45
22. Bourges H, Halhali A. 1993. Hypothesis to explain the association between hypocalciuria and low circulating 1,25-dihydroxyvitamin D levels in preeclampsia. *Med. Hypotheses* 41(3):239–43
23. Brommage R, Baxter DC, Gierke LW. 1990. Vitamin D-independent intestinal calcium and phosphate absorption during reproduction. *Am. J. Physiol.* 259(4 Pt. 1):G631–38
24. Brooke OG, Brown IR, Bone CD, Carter ND, Cleeve HJ, et al. 1980. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *Br. Med. J.* 280(6216):751–54
25. Brunvand L, Shah SS, Bergström S, Haug E. 1998. Vitamin D deficiency in pregnancy is not associated with obstructed labor. A study among Pakistani women in Karachi. *Acta Obstet. Gynecol. Scand.* 77(3):303–6
26. Camadoo L, Tibbott R, Isaza F. 2007. Maternal vitamin D deficiency associated with neonatal hypocalcaemic convulsions. *Nutr. J.* 19(6):23
27. Camargo CA Jr, Ingham T, Wickens K, Thadhani R, Silvers KM, et al. 2011. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics* 127(1):e180–87
28. Cancela L, Le Boulch N, Miravet L. 1986. Relationship between the vitamin D content of maternal milk and the vitamin D status of nursing women and breast-fed infants. *J. Endocrinol.* 110(1):43–50
29. Chan GM, Roberts CC, Folland D, Jackson R. 1982. Growth and bone mineralization of normal breast-fed infants and the effects of lactation on maternal bone mineral status. *Am. J. Clin. Nutr.* 36(3):438–43
30. Cheng MH, Wang PH. 2009. Placentation abnormalities in the pathophysiology of preeclampsia. *Expert Rev. Mol. Diagn.* 9(1):37–49
31. Clifton-Bligh RJ, McElduff P, McElduff A. 2008. Maternal vitamin D deficiency, ethnicity and gestational diabetes. *Diabet. Med.* 25(6):678–84
32. Congdon P, Horsman A, Kirby PA, Dibble J, Bashir T. 1983. Mineral content of the forearms of babies born to Asian and white mothers. *Br. Med. J.* (*Clin. Res. Ed.*) 286(6373):1233–35
33. Cranney A, Horsley T, O'Donnell S, Weiler HA, Ooi DS, et al. 2007. Effectiveness and safety of vitamin D in relation to bone health. *Evid. Rep. Technol. Assess.* (*Full Rep.*) 158. **http://www.ncbi.nlm.nih.gov/books/NBK38410**
34. Crenshaw TD, Rortvedt LA, Hassen Z. 2011. A novel pathway for vitamin D mediated phosphate homeostasis: implications for skeleton growth and mineralization. *J. Anim. Sci.* In press
35. Cross NA, Hillman LS, Allen SH, Krause GF, Vieira NE. 1995. Calcium homeostasis and bone metabolism during pregnancy, lactation, and postweaning: a longitudinal study. *Am. J. Clin. Nutr.* 61(3):514–23

36. Delvin EE, Salle BL, Glorieux FH, Adeleine P, David LS. 1986. Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. *J. Pediatr.* 109(2):328–34
37. Devereux G, Litonjua AA, Turner SW, Craig LC, McNeill G, et al. 2007. Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am. J. Clin. Nutr.* 85(3):853–59
38. Díaz L, Sánchez I, Avila E, Halhali A, Vilchis F, Larrea F. 2000. Identification of a 25-hydroxyvitamin D3 1α-hydroxylase gene transcription product in cultures of human syncytiotrophoblast cells. *J. Clin. Endocrinol. Metab.* 85(7):2543–49
39. Dick IM, Prince RL, Kelly JJ, Ho KK. 1995. Oestrogen effects on calcitriol levels in post-menopausal women: a comparison of oral versus transdermal administration. *Clin. Endocrinol.* (*Oxf.*) 43(2):219–24
40. Erkola M, Kaila M, Nwaru BI, Kronberg-Kippilä C, Ahonen S, et al. 2009. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin. Exp. Allergy* 39(6):875–82
41. Farrant HJ, Krishnaveni GV, Hill JC, Boucher BJ, Fisher DJ, et al. 2008. Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size. *Eur. J. Clin. Nutr.* 63(5):646–52
42. Frølich A, Rudnicki M, Storm T, Rasmussen N, Hegedüs L. 1992. Impaired 1,25-dihydroxyvitamin D production in pregnancy-induced hypertension. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 47(1):25–29
43. Fronczak CM, Barón AE, Chase HP, Ross C, Brady HL, et al. 2003. In utero dietary exposures and risk of islet autoimmunity in children. *Diabetes Care* 26(12):3237–42
44. Fudge NJ, Kovacs CS. 2010. Pregnancy up-regulates intestinal calcium absorption and skeletal mineralization independently of the vitamin D receptor. *Endocrinology* 151(3):886–95
45. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN. 2008. Maternal vitamin D status during pregnancy and child outcomes. *Eur. J. Clin. Nutr.* 62(1):68–77
46. Gertner JM, Coustan DR, Kliger AS, Mallette LE, Ravin N, Broadus AE. 1986. Pregnancy as state of physiologic absorptive hypercalciuria. *Am. J. Med.* 81(3):451–56
47. Ginde AA, Sullivan AF, Mansbach JM, Camargo CA Jr. 2010. Vitamin D insufficiency in pregnant and nonpregnant women of childbearing age in the United States. *Am. J. Obstet. Gynecol.* 202(5):436.e1–8
48. Greer FR, Tsang RC, Searcy JE, Levin RS, Steichen JJ. 1982. Mineral homeostasis during lactation—relationship to serum 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, parathyroid hormone and calcitonin. *Am. J. Clin. Nutr.* 36(3):431–37
49. Gupta MM, Kuppuswamy G, Subramanian AR. 1982. Transplacental transfer of 25-hydroxycholecalciferol. *Postgrad. Med. J.* 58(681):408–10
50. Haddad JG Jr, Walgate J. 1976. Radioimmunoassay of the binding protein for vitamin D and its metabolites in human serum: concentrations in normal subjects and patients with disorders of mineral homeostasis. *J. Clin. Invest.* 58(5):1217–22
51. Halhali A, Bourges H, Carrillo A, Garabedian M. 1995. Lower circulating insulin-like growth factor I and 1,25-dihydroxyvitamin D levels in preeclampsia. *Rev. Invest. Clin.* 47(4):259–66
52. Halhali A, Díaz L, Avila E, Ariza AC, Garabédian M, Larrea F. 2007. Decreased fractional urinary calcium excretion and serum 1,25-dihydroxyvitamin D and IGF-I levels in preeclampsia. *J. Steroid Biochem. Mol. Biol.* 103(3–5):803–6
53. Halhali A, Díaz L, Sánchez I, Garabédian M, Bourges H, Larrea F. 1999. Effects of IGF-I on 1,25-dihydroxyvitamin D(3) synthesis by human placenta in culture. *Mol. Hum. Reprod.* 5(8):771–76
54. Halhali A, Tovar AR, Torres N, Bourges H, Garabedian M, Larrea F. 2000. Preeclampsia is associated with low circulating levels of insulin-like growth factor I and 1,25-dihydroxyvitamin D in maternal and umbilical cord compartments. *J. Clin. Endocrinol. Metab.* 85(5):1828–33
55. Halhali A, Villa AR, Madrazo E, Soria MC, Mercado E, et al. 2004. Longitudinal changes in maternal serum 1,25-dihydroxyvitamin D and insulin like growth factor I levels in pregnant women who developed preeclampsia: comparison with normotensive pregnant women. *J. Steroid Biochem. Mol. Biol.* 89–90(1–5):553–56
56. Halloran BP, DeLuca HF. 1980. Calcium transport in small intestine during pregnancy and lactation. *Am. J. Physiol.* 239(1):E64–68

57. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. 2003. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am. J. Clin. Nutr.* 77:204–10
58. Heaney RP, Skillman TG. 1971. Calcium metabolism in normal human pregnancy. *J. Clin. Endocrinol. Metab.* 33(4):661–70
59. Hensel KJ, Randis TM, Gelber SE, Ratner AJ. 2011. Pregnancy-specific association of vitamin D deficiency and bacterial vaginosis. *Am. J. Obstet. Gynecol.* 204(1):41.e1–9
60. Hewison M. 2010. Vitamin D and the immune system: new perspectives on an old theme. *Endocrinol. Metab. Clin. North Am.* 39(2):365–79
61. Hollis BW, Pittard WB 3rd, Reinhardt TA. 1986. Relationships among vitamin D, 25-hydroxyvitamin D, and vitamin D-binding protein concentrations in the plasma and milk of human subjects. *J. Clin. Endocrinol. Metab.* 62(1):41–44
62. Hollis BW, Roos BA, Draper HH, Lambert PW. 1981. Vitamin D and its metabolites in human and bovine milk. *J. Nutr.* 111(7):1240–48
63. Hollis BW, Wagner CL. 2004. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am. J. Clin. Nutr.* 80(6 Suppl.):1752–58S
64. Hoogenboezem T, Degenhart HJ, de Muinck Keizer-Schrama SM, Bouillon R, Grose WF, et al. 1989. Vitamin D metabolism in breast-fed infants and their mothers. *Pediatr. Res.* 25(6):623–28
65. Huppertz B. 2008. Placental origins of preeclampsia: challenging the current hypothesis. *Hypertension* 51(4):970–75
66. Inst. Med. 2011. *Dietary Reference Intakes for Calcium and Vitamin D.* Washington, DC: Natl. Acad. Sci. Press
67. Ishida M, Shima M, Seino Y. 1988. 1,25(OH)2D and 24,25(OH)2D production in the developing kidney. *Pediatr. Nephrol.* 2(1):166–70
68. Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, et al. 2006. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet* 367(9504):36–43; erratum *Lancet* 367(9521):1486
69. Johnson DD, Wagner CL, Hulsey TC, McNeil RB, Ebeling M, Hollis BW. 2010. Vitamin D deficiency and insufficiency is common during pregnancy. *Am. J. Perinatol.* 28(1):7–12
70. Jones G. 2008. Pharmacokinetics of vitamin D toxicity. *Am. J. Clin. Nutr.* 88(2):582–86S
71. Kalkwarf HJ, Specker BL, Heubi JE, Vieira NE, Yergers AI. 1996. Intestinal calcium absorption during and after lactation. *Am. J. Clin. Nutr.* 63:526–31
72. Kamao M, Tsugawa N, Suhara Y, Wada A, Mori T, et al. 2007. Quantification of fat-soluble vitamins in human breast milk by liquid chromatography-tandem mass spectrometry. *Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 859(2):192–200
73. Katikaneni R, Ponnapakkam T, Ponnapakkam A, Gensure R. 2009. Breastfeeding does not protect against urinary tract infection in the first 3 months of life, but vitamin D supplementation increases the risk by 76%. *Clin. Pediatr. (Phila.)* 48(7):750–75
74. Lalau JD, Jans I, el Esper N, Bouillon R, Fournier A. 1993. Calcium metabolism, plasma parathyroid hormone, and calcitriol in transient hypertension of pregnancy. *Am. J. Hypertens.* 6(6 Pt. 1):522–27
75. Leffelaar ER, Vrijkotte TG, van Eijsden M. 2010, 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.* 104(1):108–17
76. Leung PS, Cheng Q. 2010. The novel roles of glucagon-like peptide-1, angiotensin II, and vitamin D in islet function. *Adv. Exp. Med. Biol.* 654:339–61
77. Lichtenstein P, Specker BL, Tsang RC, Mimouni F, Gormley C. 1986. Calcium-regulating hormones and minerals from birth to 18 months of age: a cross-sectional study. I. Effects of sex, race, age, season, and diet on vitamin D status. *Pediatrics* 77(6):883–90
78. Linday LA, Shindledecker RD, Greer FR, Holick MF. 2010. Commentary on "Breastfeeding does not protect against urinary tract infection in the first 3 months of life, but vitamin D supplementation increases the risk by 76%." *Clin. Pediatr. (Phila.)* 49(1):93–94

79. Liu N, Kaplan AT, Low J, Nguyen L, Liu GY, et al. 2009. Vitamin D induces innate antibacterial responses in human trophoblasts via an intracrine pathway. *Biol. Reprod.* 80(3):398–406
80. Maghbooli Z, Hossein-Nezhad A, Karimi F, Shafaei AR, Larijani B. 2008. Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. *Diabetes Metab. Res. Rev.* 24(1):27–32
81. Mahon P, Harvey N, Crozier S, Inskip H, Robinson S, et al. 2010. Low maternal vitamin D status and fetal bone development: cohort study. *J. Bone Miner. Res.* 25(1):14–19
82. Maiya S, Sullivan I, Allgrove J, Yates R, Malone M, et al. 2008. Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. *Heart* 94(5):581–84
83. Mallet E, Gügi B, Brunelle P, Hénocq A, Basuyau JP, Lemeur H. 1986. Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstet. Gynecol.* 68(3):300–4
84. Marjamäki L, Niinistö S, Kenward MG, Uusitalo L, Uusitalo U, et al. 2010. Maternal intake of vitamin D during pregnancy and risk of advanced beta cell autoimmunity and type 1 diabetes in offspring. *Diabetologia* 53(8):1599–607
85. Markestad T. 1983. Plasma concentrations of vitamin D metabolites in unsupplemented breast-fed infants. *Eur. J. Pediatr.* 141(2):77–80
86. Marya RK, Rathee S, Lata V, Mudgil S. 1981. Effects of vitamin D supplementation in pregnancy. *Gynecol. Obstet. Invest.* 12(3):155–61
87. Marya RK, Rathee S, Manrow M. 1987. Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. *Gynecol. Obstet. Invest.* 24(1):38–42
88. Maxwell JP, Miles LM. 1925. Osteomalacia in China. *Proc. R. Soc. Med.* 18(Obstet. Gynaecol. Sect.):48–66
89. McGrath JJ, Barnett AG, Eyles DW. 2005. The association between birth weight, season of birth and latitude. *Ann. Hum. Biol.* 32(5):547–59
90. Mehta S, Hunter DJ, Mugusi FM, Spiegelman D, Manji KP, et al. 2009. Perinatal outcomes, including mother-to-child transmission of HIV, and child mortality and their association with maternal vitamin D status in Tanzania. *J. Infect. Dis.* 200(7):1022–30
91. Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF. 2009. Association between vitamin D deficiency and primary cesarean section. *J. Clin. Endocrinol. Metab.* 94(3):940–45
92. Miyake Y, Sasaki S, Tanaka K, Hirota Y. 2010. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. *Eur. Respir. J.* 35(6):1228–34
93. More C, Bettembuk P, Bhattoa HP, Balogh A. 2001. The effects of pregnancy and lactation on bone mineral density. *Osteoporos. Int.* 12(9):732–37
94. More C, Bhattoa HP, Bettembuk P, Balogh A. 2003. The effects of pregnancy and lactation on hormonal status and biochemical markers of bone turnover. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 10;106(2):209–13
95. Morley R, Carlin JB, Pasco JA, Wark JD. 2006. Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. *J. Clin. Endocrinol. Metab.* 91(3):906–12
96. Morley R, Carlin JB, Pasco JA, Wark JD, Ponsonby AL. 2009. Maternal 25-hydroxyvitamin D concentration and offspring birth size: effect modification by infant VDR genotype. *Eur. J. Clin. Nutr.* 63(6):802–4
97. Namgung R, Tsang RC, Lee C, Han DG, Ho ML, Sierra RI. 1998. Low total body bone mineral content and high bone resorption in Korean winter-born versus summer-born newborn infants. *J. Pediatr.* 132(3 Pt. 1):421–25
98. Novakovic B, Sibson M, Ng HK, Manuelpillai U, Rakyan V, et al. 2009. Placenta-specific methylation of the vitamin D 24-hydroxylase gene: implications for feedback autoregulation of active vitamin D levels at the fetomaternal interface. *J. Biol. Chem.* 284(22):14838–48
99. Nwaru BI, Ahonen S, Kaila M, Erkkola M, Haapala AM, et al. 2010. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. *Pediatr. Allergy Immunol.* 21(1 Pt. 1):29–37
100. O'Brien KO, Donangelo CM, Zapata CL, Abrams SA, Spencer EM, King JC. 2006. Bone calcium turnover during pregnancy and lactation in women with low calcium diets is associated with calcium intake and circulating insulin-like growth factor 1 concentrations. *Am. J. Clin. Nutr.* 83(2):317–23

101. Olafsdottir AS, Wagner KH, Thorsdottir I, Elmadfa I. 2001. Fat-soluble vitamins in the maternal diet, influence of cod liver oil supplementation and impact of the maternal diet on human milk composition. *Ann. Nutr. Metab.* 45(6):265–72
102. Papapetrou PD. 2010. The interrelationship of serum 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and 24,25-dihydroxyvitamin D in pregnancy at term: a meta-analysis. *Hormones* (*Athens*) 9(2):136–44
103. Park MJ, Namgung R, Kim DH, Tsang RC. 1998. Bone mineral content is not reduced despite low vitamin D status in breast milk-fed infants versus cow's milk based formula-fed infants. *J. Pediatr.* 132(4):641–45
104. Park W, Paust H, Kaufmann HJ, Offermann G. 1987. Osteomalacia of the mother—rickets of the newborn. *Eur. J. Pediatr.* 146(3):292–93
105. Pearson D, Kaur M, San P, Lawson N, Baker P, Hosking D. 2004. Recovery of pregnancy mediated bone loss during lactation. *Bone* 34(3):570–78
106. Peris P, Guañabens N, Monegal A, Pons F, Martínez de Osaba MJ, et al. 2002. Pregnancy associated osteoporosis: the familial effect. *Clin. Exp. Rheumatol.* 20(5):697–700
107. Powe CE, Seely EW, Rana S, Bhan I, Ecker J, et al. 2010. First trimester vitamin D, vitamin D binding protein, and subsequent preeclampsia. *Hypertension* 56(4):758–63
108. Prentice A. 2008. Vitamin D deficiency: a global perspective. *Nutr. Rev.* 66(Suppl. 2):S153–64
109. Prentice A, Jarjou LM, Goldberg GR, Bennett J, Cole TJ, Schoenmakers I. 2009. Maternal plasma 25-hydroxyvitamin D concentration and birth weight, growth and bone mineral accretion of Gambian infants. *Acta Paediatr.* 98(8):1360–62
110. Prentice A, Schoenmakers I, Laskey MA, de Bono S, Ginty F, Goldberg GR. 2007. Nutrition and bone growth and development. *Proc. Nutr. Soc.* 65(4):348–60
111. Prentice A, Yan L, Jarjou LM, Dibba B, Laskey MA, et al. 1997. Vitamin D status does not influence the breast-milk calcium concentration of lactating mothers accustomed to a low calcium intake. *Acta Paediatr.* 86(9):1006–8
112. Ramos-Lopez E, Kahles H, Weber S, Kukic A, Penna-Martinez M, et al. 2008. Gestational diabetes mellitus and vitamin D deficiency: genetic contribution of CYP27B1 and CYP2R1 polymorphisms. *Diabetes Obes. Metab.* 10(8):683–85
113. Ritchie LD, Fung EB, Halloran BP, Turnlund JR, Van Loan MD, et al. 1998. A longitudinal study of calcium homeostasis during human pregnancy and lactation and after resumption of menses. *Am. J. Clin. Nutr.* 67(4):693–701
114. Ron M, Levitz M, Chuba J, Dancis J. 1984. Transfer of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 across the perfused human placenta. *Am. J. Obstet. Gynecol.* 148(4):370–74
115. Rothberg AD, Pettifor JM, Cohen DF, Sonnendecker EW, Ross FP. 1982. Maternal-infant vitamin D relationships during breast-feeding. *J. Pediatr.* 101(4):500–3
116. Sanchez PA, Idrisa A, Bobzom DN, Airede A, Hollis BW, et al. 1997. Calcium and vitamin D status of pregnant teenagers in Maiduguri, Nigeria. *J. Natl. Med. Assoc.* 89(12):805–11
117. Schnatz PF, Barker KG, Marakovits KA, O'Sullivan DM. 2010. Effects of age at first pregnancy and breast-feeding on the development of postmenopausal osteoporosis. *Menopause* 17(6):1161–66
118. Schnatz PF, Marakovits KA, O'Sullivan DM. 2010. Assessment of postmenopausal women and significant risk factors for osteoporosis. *Obstet. Gynecol. Surv.* 65(9):591–96
119. Scholl TO, Chen X. 2009. Vitamin D intake during pregnancy: association with maternal characteristics and infant birth weight. *Early Hum. Dev.* 85(4):231–34
120. Seely EW, Brown EM, DeMaggio DM, Weldon DK, Graves SW. 1997. A prospective study of calciotropic hormones in pregnancy and post partum: reciprocal changes in serum intact parathyroid hormone and 1,25-dihydroxyvitamin D. *Am. J. Obstet. Gynecol.* 176(1 Pt. 1):214–17
121. Seely EW, Wood RJ, Brown EM, Graves SW. 1992. Lower serum ionized calcium and abnormal calciotropic hormone levels in preeclampsia. *J. Clin. Endocrinol. Metab.* 74(6):1436–40
122. Shand AW, Nassar N, Von Dadelszen P, Innis SM, Green TJ. 2010. Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for pre-eclampsia. *BJOG* 117(13):1593–98
123. Smith R, Athanasou NA, Ostlere SJ, Vipond SE. 1995. Pregnancy-associated osteoporosis. *QJM* 88(12):865–78

124. Smith R, Stevenson JC, Winearls CG, Woods CG, Wordsworth BP. 1985. Osteoporosis of pregnancy. *Lancet* 1(8439):1178–80
125. Sowers M, Zhang D, Hollis BW, Shapiro B, Janney CA, et al. 1998. Role of calciotrophic hormones in calcium mobilization of lactation. *Am. J. Clin. Nutr.* 67(2):284–91
126. Specker BL, Ho ML, Oestreich A, Yin TA, Shui QM, et al. 1992. Prospective study of vitamin D supplementation and rickets in China. *J. Pediatr.* 120(5):733–39
127. Specker BL, Tsang RC, Hollis BW. 1985. Effect of race and diet on human-milk vitamin D and 25-hydroxyvitamin D. *Am. J. Dis. Child.* 139(11):1134–37
128. Steichen JJ, Tsang RC, Gratton TL, Hamstra A, DeLuca HF. 1980. Vitamin D homeostasis in the perinatal period: 1,25-dihydroxyvitamin D in maternal, cord, and neonatal blood. *N. Engl. J. Med.* 302(6):315–19
129. Takeuchi A, Okano T, Tsugawa N, Tasaka Y, Kobayashi T, et al. 1989. Effects of ergocalciferol supplementation on the concentration of vitamin D and its metabolites in human milk. *J. Nutr.* 119(11):1639–46
130. Thandrayen K, Pettifor JM. 2010. Maternal vitamin D status: implications for the development of infantile nutritional rickets. *Endocrinol. Metab. Clin. North Am.* 39(2):303–20
131. Tran HA, Petrovsky N. 2002. Pregnancy-associated osteoporosis with hypercalcaemia. *Intern. Med. J.* 32(9–10):481–85
132. Turner M, Barré PE, Benjamin A, Goltzman D, Gascon-Barré M. 1988. Does the maternal kidney contribute to the increased circulating 1,25-dihydroxyvitamin D concentrations during pregnancy? *Miner. Electrolyte Metab.* 14(4):246–52
133. Uemura H, Yasui T, Kiyokawa M, Kuwahara A, Ikawa H, et al. 2002. Serum osteoprotegerin/osteoclastogenesis-inhibitory factor during pregnancy and lactation and the relationship with calcium-regulating hormones and bone turnover markers. *J. Endocrinol.* 174(2):353–59
134. van Hoof HJ, de Sévaux RG, van Baelen H, Swinkels LM, Klipping C, et al. 2001. Relationship between free and total 1,25-dihydroxyvitamin D in conditions of modified binding. *Eur. J. Endocrinol.* 144(4):391–96
135. Viganò P, Lattuada D, Mangioni S, Ermellino L, Vignali M, et al. 2006. Cycling and early pregnant endometrium as a site of regulated expression of the vitamin D system. *J. Mol. Endocrinol.* 36(3):415–24
136. Viljakainen HT, Korhonen T, Hytinantti T, Laitinen EK, Andersson S, et al. 2011. Maternal vitamin D status affects bone growth in early childhood—a prospective cohort study. *Osteoporos Int.* 22:883–91
137. Viljakainen HT, Saarnio E, Hytinantti T, Miettinen M, Surcel H, et al. 2010. Maternal vitamin D status determines bone variables in the newborn. *J. Clin. Endocrinol. Metab.* 95(4):1749–57
138. Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW. 2006. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeed. Med.* 1(2):59–70
139. Weisman Y, Harell A, Edelstein S, David M, Spirer Z, Golander A. 1979. 1 alpha, 25-Dihydroxyvitamin D3 and 24,25-dihydroxyvitamin D3 in vitro synthesis by human decidua and placenta. *Nature* 27;281(5729):317–19
140. Wilson SG, Retallack RW, Kent JC, Worth GK, Gutteridge DH. 1990. 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.)* 32(5):613–22
141. Yetley EA. 2008. Assessing the vitamin D status of the US population. *Am. J. Clin. Nutr.* 88(2):483–90S
142. Yu CK, Sykes L, Sethi M, Teoh TG, Robinson S. 2009. Vitamin D deficiency and supplementation during pregnancy. *Clin. Endocrinol. (Oxf.)* 70(5):685–90
143. Zehnder D, Evans KN, Kilby MD, Bulmer JN, Innes BA, et al. 2002. The ontogeny of 25-hydroxyvitamin D(3) 1alpha-hydroxylase expression in human placenta and decidua. *Am. J. Pathol.* 161(1):105–14
144. Zeni SN, Ortela Soler CR, Lazzari A, López L, Suarez M, et al. 2003. Interrelationship between bone turnover markers and dietary calcium intake in pregnant women: a longitudinal study. *Bone* 33(4):606–13

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Errata

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