Implications of vitamin D deficiency in pregnancy and lactation

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Vitamin D deficiency has long been associated with poor bone development and has been identified as the cause of rickets. Although the incidence of rickets has declined with the current daily recommendations of vitamin D intake, the prevalence and additional consequences of low serum vitamin D levels have not been recognized until recently. The measurement of serum vitamin D in pregnancy has helped researchers establish the prevalence of vitamin D deficiency and elucidate adverse maternal and fetal outcomes associated with it. Prevention of these diseases and reduction of the risk for childhood illnesses that are linked to early vitamin D deficiency are possible with greater understanding of vitamin D physiologic components, risk factors for vitamin D deficiency, and methods of supplementation to attain optimal levels in pregnant and lactating women.

Vitamin D is an essential fat soluble vitamin and a key modulator of calcium metabolism in children and adults. Because calcium demands increase in the third trimester of pregnancy, vitamin D status becomes crucial for maternal health, fetal skeletal growth, and optimal maternal and fetal outcomes. Vitamin D deficiency is common in pregnant women (5-50%) and in breastfed infants (10-56%), despite the widespread use of prenatal vitamins, because these are inadequate to maintain normal vitamin D levels (≥32 ng/mL). Adverse health outcomes such as preeclampsia, low birthweight, neonatal hypocalcemia, poor postnatal growth, bone fragility, and increased incidence of autoimmune diseases have been linked to low vitamin D levels during pregnancy and infancy. Studies are underway to establish the recommended daily doses of vitamin D in pregnant women. This review discusses vitamin D metabolism and the implications of vitamin D deficiency in pregnancy and lactation.

Key words: lactation, pregnancy, vitamin D deficiency

Vitamin D and calcium metabolism in pregnancy

During pregnancy and lactation, significant changes in maternal vitamin D and calcium metabolism occur to provide the calcium that is needed for fetal bone mineral accretion. During the first trimester, the fetus accumulates 2-3 mg/d in the skeleton; however, this rate of accumulation doubles in the last trimester. The body of a pregnant woman adapts to fetal requirements by increasing calcium absorption in early pregnancy, with maximal absorption in the last trimester. Along with the transfer of calcium to the fetus, the increased intestinal absorption is balanced by enhancing urinary calcium excretion, thereby keeping serum ionized calcium stable throughout pregnancy. In several small studies, 1,25(OH)2D levels in plasma increased by 2-fold early in pregnancy, compared with prepregnancy values, reached a maximum in the third trimester, and returned to normal or below normal during lactation. Plasma 25(OH)D levels do not change, unless intake or synthesis changes. The increased 1,25(OH)2D synthesis depends on the acceleration of 1α-hydroxylation in the maternal kidneys and activity, thereby increasing calcium and phosphorous availability in the blood (Figure).17,20

### Table 1: Vitamin D content

<table>
<thead>
<tr>
<th>Source of vitamin D</th>
<th>Amount of vitamin D (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s milk, fortified with vitamin D, 8 oz</td>
<td>98</td>
</tr>
<tr>
<td>Soy milk, fortified with vitamin D, 8 oz</td>
<td>100</td>
</tr>
<tr>
<td>Orange juice, fortified, 8 oz</td>
<td>100</td>
</tr>
<tr>
<td>Cereal, fortified, 1 cup</td>
<td>40-50</td>
</tr>
<tr>
<td>Pink salmon, canned, 3 oz</td>
<td>530</td>
</tr>
<tr>
<td>Sardines, canned, 3 oz</td>
<td>231</td>
</tr>
<tr>
<td>Mackerel, 3 oz</td>
<td>306</td>
</tr>
<tr>
<td>Herring, 3 oz</td>
<td>1,383</td>
</tr>
<tr>
<td>Tuna, canned in oil, 3 oz</td>
<td>200</td>
</tr>
<tr>
<td>Quaker Nutrition for Women Instant Oatmeal, 1 packet</td>
<td>154</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>25</td>
</tr>
<tr>
<td>Most multivitamins</td>
<td>400</td>
</tr>
<tr>
<td>Tri-Vi-Sol infant supplements, 1 drop</td>
<td>400</td>
</tr>
<tr>
<td>Prenatal vitamins</td>
<td>400</td>
</tr>
<tr>
<td>Over-the-counter vitamin D3 supplements, 2000 (max)</td>
<td></td>
</tr>
<tr>
<td>Typical prescribed vitamin D3 supplements for deficiency</td>
<td>50,000 (given weekly until replete)</td>
</tr>
</tbody>
</table>

Quaker, Quaker Oats Co, Chicago, IL; Tri-Vi-Sol; Mead Johnson Pharmaceuticals, Evansville, IN.


The efficiency of vitamin D synthesis depends on a variety of factors, most importantly the number of UVB photons that penetrate the epidermis. More time spent indoors and widespread use of sunscreen have resulted in reduced sun exposure and less vitamin D production. Latitude and season of the year also determine both the quantity and quality of UVB radiation. Skin production of vitamin D declines after August and virtually ceases from November until March at latitudes of >42° N (Boston). Other factors, such as aging and increased melanin in dark-skinned people, reduce the efficiency by which sunlight converts provitamin D, thereby decreasing vitamin D synthesis (Table 2). Plasma 25(OH)D levels during the winter therefore depend on vitamin D intake, which is largely from food additives or supplements.

As an individual becomes deficient in vitamin D, intestinal calcium and phosphorous absorption decrease; serum ionized calcium levels drop, and synthesis of parathyroid hormone (PTH) is stimulated. Increased plasma PTH maintains serum calcium in the normal range by enhancing renal production of 1,25(OH)2D, increasing bone turnover, accelerating bone loss, and promoting tubular calcium reabsorption and phosphate excretion. Increased 1,25(OH)2D induces intestinal calcium and phosphorus absorption and stimulates osteoclast

### Table 2: Risk factors for vitamin D deficiency

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Northern latitudes, especially winter or spring</td>
</tr>
<tr>
<td>Limited sun exposure</td>
</tr>
<tr>
<td>Regular use of sunscreens</td>
</tr>
<tr>
<td>African American or dark skin</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Extensive clothing cover</td>
</tr>
<tr>
<td>Aging</td>
</tr>
<tr>
<td>Malabsorptive syndromes (cystic fibrosis, cholestatic liver disease, inflammatory bowel disease, short gut syndrome)</td>
</tr>
</tbody>
</table>

Vitamin D metabolism and tissue actions

25(OH)D, 25-hydroxy vitamin D; Ca\(^{2+}\), calcium; CRP, C-reactive protein; DBP, vitamin D binding protein; DM, diabetes mellitus; MMP9, matrix metalloproteinase 9; PO4, phosphate; PTH, parathyroid hormone; SGA, small for gestational age; UVB, ultraviolet B.

possibly increased placental and decidual 1α-hydroxylase activity.\textsuperscript{30-32} The stimulus to increase synthesis of 1,25(OH)\textsubscript{2}D is not clear because serum PTH levels do not change during pregnancy. A potential signal for placental calcium transfer and placental synthesis of active vitamin D is PTH-related peptide (PTHrP), which is produced in fetal parathyroid glands and the placental tissues and increases placental synthesis of active vitamin D.\textsuperscript{33-36} PTHrP potentially might reach the maternal circulation. Acting through the PTH/PTHrP receptor in kidney and bone, PTHrP could mediate the increased 1,25(OH)\textsubscript{2}D and help to regulate calcium and PTH levels during human pregnancy.\textsuperscript{37} The profound increase in intestinal calcium absorption cannot be explained solely by the increased 1,25(OH)\textsubscript{2}D because the increased calcium absorption occurs before 1,25(OH)\textsubscript{2}D levels increase and occurs in rodents even in the absence of vitamin D receptor.\textsuperscript{38}

Other signals that regulate active calcium homeostasis and vitamin D synthesis during pregnancy include prolactin, placental lactogen, calcitonin, osteoprotegerin, and estrogen. Prolactin increases throughout pregnancy and remains above normal after delivery. Placental lactogen increases throughout pregnancy but returns to prepregnancy values after delivery. Prolactin and placental lactogen’s roles have not been clearly elucidated in calcium metabolism. It is thought that they both contribute to increase calcium absorption from the intestine, decrease urinary calcium excretion, and stimulate production of PTHrP and 1,25(OH)\textsubscript{2}D.\textsuperscript{39,40} Calcitonin increases 2-fold in the second trimester, compared with the first trimester, but then declines slightly at term. It has been hypothesized that the rise in serum calcitonin protects the maternal skeleton from excessive resorption of calcium.\textsuperscript{41} Osteoprotegerin levels have also been shown to be higher in the third trimester of pregnancy than the first trimester of pregnancy. The fetal skeleton contains 30 g of calcium, most of which is deposited during the third trimester of pregnancy. It can be inferred that osteoprotegerin, which acts as a decoy receptor for RANK ligand and inhibits osteoclast activity, may also protect the maternal skeleton from excessive resorption of calcium.\textsuperscript{42,43} Lactation is a time of relative estrogen deficiency because of elevated prolactin levels that suppress the release of gonadotropins and, in turn, estrogen and perhaps stimulate the release of PTHrP. Estrogen deficiency leads to bone resorption and suppression of PTH levels. PTHrP levels are elevated and act as a surrogate for PTH, thereby allowing continued absorption of calcium from the urine and bone resorption.\textsuperscript{38,44}

### Classification of vitamin D status

Vitamin D status is usually estimated by measuring the level of plasma 25(OH)D. Evidence of 25(OH)D concentrations of 44-70 ng/mL observed in healthy outdoor workers (such as farmers and lifeguards) suggest an optimal healthy level that is far above the levels that are reported to prevent rickets and osteomalacia.\textsuperscript{45,46} Studies that have evaluated the correlation between vitamin D levels and intestinal calcium absorption, maximal PTH suppression, bone fracture prevention, and bone turnover have helped to develop a classification of stages for vitamin D status in nonpregnant adults (Table 3) that indicate that levels of >32 ng/mL are required for adequacy.\textsuperscript{47,48} These stages correlate with maternal and fetal outcomes, which suggests that they also apply in pregnancy and during lactation.\textsuperscript{49}

### Prevalence of vitamin D deficiency in pregnancy

Vitamin D deficiency during pregnancy is a worldwide epidemic; studies have reported a prevalence that ranges from 18-84%, depending on the country of residence and local clothing customs.\textsuperscript{50-54} In the United States, vitamin D deficiency is estimated to occur in 5-50% of pregnant women.\textsuperscript{55,56} African American women have a much higher risk of vitamin D deficiency, compared with other women because of increased skin pigmentation and low dietary intake.\textsuperscript{57} Bodnar et al\textsuperscript{13} reported the prevalence of vitamin D deficiency and insufficiency in 200 white and 200 black pregnant women and in the cord blood of their neonates. In African American pregnant women, vitamin D deficiency and insufficiency oc-
curred in 29.2% and 54.1%, respectively, compared with 5% and 42.1% of white pregnant women. Interestingly, 90% of study participants reported that they were taking prenatal vitamins. At delivery, vitamin D deficiency and insufficiency occurred in 45.6% and 46.8% of black neonates, respectively, compared with 9.7% and 56.4% of white neonates.

**Maternal effects of vitamin D deficiency**

Preeclampsia and hypertensive disorders complicate 3-10% of pregnancies in the United States and contribute to maternal and neonatal morbidity and deaths.58,59 Previous studies have shown that women with preeclampsia have lower urinary calcium excretion, lower ionized calcium levels, higher PTH levels, and lower 1,25 (OH)₂ D₃ levels, compared with normotensive pregnant control subjects.60 Low plasma calcium levels induce several common mechanisms that are associated with hypertension, such as increasing renal renin and PTH levels.61,62 It is thought that placental defects that cause decreased synthesis of active vitamin D could be a key event in the development of this disease by contributing to decreased calcium levels.63

A recent study in 274 pregnant women showed that vitamin D deficiency at or before week 22 of gestation was an independent predictor of preeclampsia and low vitamin D status in the neonate. Patients with 25(OH)D levels <15 ng/mL had a 5-fold increase in the risk of preeclampsia, despite receiving prenatal vitamins (adjusted odds ratio, 5.0; 95% confidence interval, 1.7–14.1).64 In addition, 2 interventional trials have reported the effects of vitamin D plus calcium supplementation on blood pressure outcomes. One study showed that halibut liver oil supplementation (900 IU of vitamin D per day) beginning at week 20 of gestation decreased the odds of preeclampsia by 32%, but these women were receiving a dietary supplement that contained other vitamins, minerals, and fish oil in addition to the halibut liver oil.64 A second randomized controlled clinical trial demonstrated that vitamin D (1200 IU/d) plus calcium (375 mg/d) started at 20-24 weeks of gestation significantly reduced blood pressure (P < .001), compared with placebo treatment, but the difference in the incidence of preeclampsia between the 2 groups was not statistically significant.65,66

It is hypothesized that low calcium levels, perhaps through vitamin D mediation, ultimately lead to the development of preeclampsia. Women in the United States, however, are not at risk for calcium deficiency.67 The Calcium for Preeclampsia Prevention study, which was conducted in the United States, showed no decrease in the risk of the development of preeclampsia with calcium supplementation. An international study supplemented calcium to women with low calcium intakes (<600 mg/d) and found no reduction in the rate of preeclampsia but did show a reduction in the severity of the disease.68 Based on results of the aforementioned trials, the exact role that calcium and vitamin D play in the development and severity of preeclampsia is still unclear. A large interventional trial is needed to further elucidate whether calcium supplementation, vitamin D supplementation, or both can reduce the incidence of this disease.

**Fetal and newborn effects of gestational vitamin D deficiency**

**Infant size**

Several studies have reported an association between infant size and vitamin D status. In a study in 449 Iranian pregnant women, higher mean birth length was found at delivery in babies from mothers who received the recommended dietary allowance of calcium and vitamin D. The incidence of low birthweight was significantly lower in newborn infants from mothers who received the recommended doses of calcium and vitamin D.69 In 2251 pregnant women from the Camden study, a prospective analysis of the effects of maternal nutrition and growth in generally healthy pregnant women in the United States, total intake of vitamin D was a significant predictor of infant birthweight when adjusted for gestational duration. After data adjustments for energy intake, other nutrients (calcium, iron, folate, protein, zinc), and other potential confounding variables, a significant direct trend between birthweight and vitamin D intake persisted. In addition, pregnant women with vitamin D intakes <200 IU/d had infants with birthweights that were 60 g below women with vitamin D intakes at or above 200 IU/d.29 However, studies that account for confounding variables (such as ethnicity, nutritional status, and sunlight exposure) are needed.

Initial randomized controlled trials of vitamin D supplementation in British mothers of Asian descent suggest a greater incidence of small-for-gestational-age infants born to mothers who received placebo than to mothers who received 1000 IU of vitamin D per day during the final trimester of pregnancy.71,72 Follow-up data from the same group of patients showed that infants from the maternal placebo group gained less weight and had a lower rate of linear growth in the first year of life than infants from the supplemented group.73 In contrast, a randomized trial was conducted in France in 3 groups of pregnant women in the third trimester: 1 group received 200,000 IU of vitamin D in a single dose, 1 group received 1000 IU of vitamin D daily, and 1 group served as the control. No differences in birthweight were found among groups.74 However, these studies are based on small sample sizes, which makes interpretation difficult.

Recent studies with larger patient samples suggest that both milk consumption and vitamin D intake are predictors of infant size. One study showed that, for every cup of milk consumed per day by the mother, there is an associated increase in infant birthweight of 41 g and that every microgram of daily vitamin D intake correlates with an increased birthweight of 11 g.75 A study of >50,000 women from the Netherlands showed that those women who drank a significant amount of milk (≥6 glasses per day) had an odds ratio of 1.59 for having a large-for-gestational age baby. Inversely, women who consumed no milk during their pregnancy had a significantly increased risk of having a small-for-gestational-age baby.76 However, multiple confounding factors could be implicated for the milk effects on gestational baby size. Larger interventional, randomized
control trials to address birth size and vitamin D are underway.

**Skeletal development**

The importance of vitamin D for fetal and infant skeletal development has long been recognized. Poor skeletal mineralization in utero that is induced by vitamin D deficiency may manifest as congenital rickets, craniotabes, or osteopenia in newborn infants. Congenital rickets is rare, typically occurring only in infants born to mothers with severe vitamin D deficiency and osteomalacia (Table 2). In full-term infants, impaired fetal bone ossification correlated with maternal vitamin D deficiency. Interestingly, reduced concentrations of 25(OH)D in mothers during late pregnancy was associated with reduced whole-body and lumbar-spine bone-mineral content in their children at age 9 years. Maternal vitamin D deficiency has also been associated with craniotabes or larger fontanelles in full-term infants, which is consistent with impaired ossification of the skull; however, these findings are controversial.

**Vitamin D deficiency during lactation**

In the first 6-8 weeks of postnatal life, the vitamin D status of a neonate is dependent largely on vitamin D that is acquired through placental transfer in utero, as evidenced by the direct linear relationship between maternal and cord blood levels of 25(OH)D. In most infants, vitamin D stores acquired from the mother are depleted by approximately 8 weeks of age. Thereafter, vitamin D is derived from diet, sunlight, and supplementation. In general, formula-fed babies receive adequate vitamin D because it is added to all formulas in the United States in amounts of 400 IU of vitamin D per liter. In contrast, babies who are exclusively breastfed are at higher risk for vitamin D deficiency. Human milk contains a very low concentration of vitamin D (approximately 20-60 IU/L), which represents 1.5-3% of the maternal level. This concentration is not sufficient to maintain an optimal vitamin D level in the baby if exposure to sunlight is limited.

Breast-fed infants from vitamin D–deficient mothers occasionally manifest life-threatening conditions such as hypocalcemic seizures and dilated cardiomyopathy. In the United Kingdom and Ireland, the incidence of rickets-associated heart failure is estimated at 2.7 cases per year. A study from Canada between 2002 and 2004 identified the incidence of vitamin D–deficient rickets in children ≤18 years old at 2.9 cases per 100,000, 19% of whom had hypocalcemic seizures overall, with seizures being the complaint in nearly one-half of infants ≤1 year old. In another case series from London between 1996 and 2001, severe vitamin D deficiency was identified in 65 children ≤16 years old, 25% of whom had seizures. Recent reports of rickets in breast-fed infants with a lack of sun exposure are concerning. All of these conditions respond to calcium and vitamin D replacement or exposure to sunlight. Therefore, as of November 2008, the American Academy of Pediatrics recommends that exclusively breast-fed infants should receive supplements that contain 400 IU of vitamin D daily, beginning shortly after birth and continuing throughout childhood and adolescence. Supplementation has traditionally been available only in liquid formulations that are administered with a dropper and that include vitamins A and C, but now liquid vitamin D is available alone without other vitamins. Recent studies show that maternal vitamin D intake of 4000 IU daily during lactation in vitamin D–insufficient mothers enhances vitamin D levels in breast milk and may be a potential therapeutic intervention to prevent vitamin D deficiency–related complications in both women and their breast-fed infants.

**Childhood illness and gestational vitamin D deficiency**

**Asthma**

Multiple biologic actions suggest a correlation between vitamin D deficiency and the asthma epidemic. Vitamin D signaling pathways and receptor polymorphisms may have effects on Th1-Th2 imbalance, smooth muscle contraction, airway inflammation, prostaglandin regulation, and airway remodeling, all of which can impact asthma control. In animal models, vitamin D regulates lung growth in utero. Clinical studies indicate an inverse association between vitamin D intake during gestation and wheezing in their children during the first years of life. Post-hoc analysis of serum samples of asthmatic children from the Childhood Asthma Management Program study showed that approximately 35% of patients had levels of vitamin D <30 ng/mL and that these children had lower lung function and greater risks for exacerbations than those with levels >30 ng/mL.

**Type 1 diabetes mellitus (type 1 DM)**

The Diabetes Autoimmunity Study in the Young reported that autoantibodies to islet cells are correlated inversely with maternal dietary vitamin D intake during pregnancy. More direct evidence of this correlation has come from the European and Diabetes study in which vitamin D supplementation during the first year of life decreased the risk of the development of type 1 DM (odds ratio, 0.67; 95% confidence interval, 0.5–0.8). In a Finnish study, children who received 2000 IU of vitamin D per day during the first year of life had an 80% reduction in the risk of the development of type 1 DM during a follow-up period of 30 years. In contrast, children who were vitamin D-deficient or who were suspected to have rickets at 1 year had a 2.4-fold increased risk of the development of type 1 DM. The high doses of vitamin D that were used in this study clearly establish the preventive effects of this vitamin in the development of type 1 DM.

**Recommendations for monitoring and replacement**

Vitamin D is important to maternal health, fetal development, and postnatal life. Current prenatal care does not include the monitoring of vitamin D levels, which is an unfortunate oversight because deficiency is easily treated. On average, daily vitamin D supplements of 1000-2000 IU cost $1-2 per month. Women with ≥1 risk factors for vitamin D deficiency (Table 2) should have a
plasma 25(OH)D level drawn at the beginning of gestation and at mid pregnancy. The recommended target range for nonpregnant adults is 32-100 ng/mL (80-250 nmol/L), which appears to be a safe range during pregnancy. In the United States, the current recommendation for vitamin D intake during pregnancy is 200-400 IU/d. However, a previous study has shown that prenatal supplements that contain 400 IU of vitamin D are not adequate to achieve normal vitamin D levels in pregnant women or their infants. Even more concerning, studies of supplementation with 800-1600 IU vitamin D per day during the last trimester of pregnancy in women with 25(OH)D levels <15 ng/mL showed that vitamin D levels increased from 5.8 ng/mL to a mere 11 ng/mL. Therefore, supplemental vitamin D in doses that exceed 1000 IU per day (2000-10,000 IU/d) may be required to achieve a normal concentration of circulating vitamin D in severely deficient patients. Studies with ≥2000-4000 IU daily of vitamin D supplementation in nonpregnant women have shown these amounts to be safe and effective at achieving normal vitamin D levels. Studies in pregnant women are underway in the United States that use vitamin D at doses of 2000 IU and 4000 IU daily to establish vitamin D recommendations during pregnancy.

Comment

Recent evidence demonstrates that the prevalence of vitamin D deficiency in the general population and in women of child-bearing age is surprisingly high. However, the influence of vitamin D deficiency on calcium metabolism during pregnancy has not been well-characterized. Vitamin D deficiency is known to be associated with an increased prevalence of preeclampsia, which is a common cause of increased mortality rates in pregnancy. In children, it is also associated with small infant size and the development of common childhood diseases, such as asthma and type 1 DM. Current recommendations for daily vitamin D intake (200 IU) are inadequate to maintain serum levels of 25(OH)D in the normal range during pregnancy and lactation. Further studies are needed to determine the serum levels and the degree of supplementation that is required to optimize maternal and fetal outcomes. However, because vitamin D supplementation is simple and cost-effective with a low likelihood of toxicity, we recommend increased supplementation in all pregnant women to keep serum levels of 25(OH)D in the normal range for adults (>32 ng/mL).

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