

OBSTETRICS

Implications of vitamin D deficiency in pregnancy and lactation

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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 that are associated with it.

Vitamin D physiologic components

The nutritional forms of vitamin D include D₃ (cholecalciferol), which is generated in the skin of humans and animals, and vitamin D₂ (ergocalciferol), which is derived from plants; both can be absorbed in the gut and used by humans. The Food and Nutrition Board's current recommendation for adequate intake of vitamin D is 200 IU/d for both pregnant and nonpregnant individuals aged 0-50 years. In the United States the major dietary sources of vitamin D are fortified foods. However, the relative contribution of dietary vitamin D is low in humans compared with endogenous production from sunlight.

The efficiency of vitamin D synthesis depends on a variety of factors, most significantly the number of ultraviolet B photons

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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.

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that penetrate the epidermis. Plasma 25-hydroxy vitamin D (25[OH]D) levels during the winter therefore depend on vitamin D intake, which is largely derived from food additives or supplements.

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. The body of a pregnant woman adapts to fetal requirements by increasing calcium absorption beginning early in pregnancy, with maximal absorption in the last trimester. In several small studies, 1,25 dihydroxyvitamin D (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. However, the profound increase in intestinal calcium absorption cannot be explained solely by the increased 1,25 (OH)₂D level because the increased calcium absorption occurs before 1,25 (OH)₂D levels increase and occurs in rodents even in the absence of a vitamin D receptor. Other signals that regulate calcium homeostasis and vitamin D synthesis

during pregnancy (such as prolactin, placental lactogen, calcitonin, osteoprotegerin, and estrogen) are also implicated, but the mechanisms are not fully understood.

Classification of vitamin D status

Vitamin D status is usually estimated by measuring the level of plasma 25(OH)D. Studies have evaluated the correlation between vitamin D levels and intestinal calcium absorption, maximal parathyroid hormone suppression, bone fracture prevention, and bone turnover have helped to develop a classification of stages for vitamin D status in nonpregnant adults (Table), which indicates that levels of >32 ng/mL are required for adequacy. In the United States, vitamin D deficiency is estimated to occur in 5-50% of pregnant women.

Maternal effects of vitamin D deficiency

Patients with 25(OH)D levels of <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). One study showed that halibut liver oil supplementation (900 IU of vitamin D per day) that was begun at week 20 of gestation decreased

TABLE
Stages of vitamin D deficiency and adverse effects

Stage	Serum 25(OH)D, ng/mL	Maternal adverse effects	Newborn infant adverse effects
Severe deficiency	<10	Increased risk of preeclampsia, calcium malabsorption, bone loss, poor weight gain, myopathy, higher parathyroid hormone levels	Small for gestational age, neonatal hypocalcemia, hypocalcemic seizures, infantile heart failure, enamel defects, large fontanelle, congenital rickets, rickets of infancy if breastfed
Insufficiency	11-32	Bone loss, subclinical myopathy	Neonatal hypocalcemia, reduced bone mineral density, rickets of infancy if breastfed
Adequacy	32-100	Adequate calcium balance, parathyroid hormone levels	None, unless exclusively breastfed
Toxicity	>100	Hypercalcemia, increased urine calcium loss	Infantile idiopathic hypercalcemia

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the odds of preeclampsia by 32%; however, these women were receiving a dietary supplement that contained other vitamins, minerals, and fish oil in addition to the halibut liver oil. 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 infant effects of gestational vitamin D deficiency

Several studies report an association between infant size and vitamin D status. Initial randomized controlled trials of vitamin D supplementation in British mothers of Asian descent suggest a greater incidence of small-for-gestational-age infants are born to mothers who received placebo than to mothers who received 1000 IU of vitamin D per day during the final trimester of pregnancy. Larger interventional, randomized control trials to address birth size and vitamin D are under way.

Poor skeletal mineralization in utero that is induced by vitamin D deficiency may manifest as congenital rickets, craniotabes, or osteopenia in newborn infants. Reduced concentrations of 25 (OH)D in mothers during late pregnancy were associated with reduced whole body and lumbar spine bone mineral content in their children at age 9 years.

Vitamin D deficiency during lactation

In most infants, vitamin D stores that are acquired from the mother are depleted by approximately 8 weeks of age. In general, formula-fed babies receive adequate vita-

min D because it is added to all formulas in the United States in amounts of 400 IU of vitamin D per liter. Human milk contains a very low concentration of vitamin D (approximately 20-60 IU/L) that represents 1.5-3% of the maternal level.

Breast-fed infants from vitamin D-deficient mothers occasionally manifest life-threatening conditions such as hypocalcemic seizures and dilated cardiomyopathy. 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.

Childhood illness and gestational vitamin D deficiency

Clinical studies indicate an inverse association between vitamin D intake during gestation and wheezing in children during the first years of life. 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 diabetes mellitus during a follow-up period of 30 years.

Recommendations for monitoring and replacement

Vitamin D is important to maternal health, fetal development, and postnatal life. Current prenatal care does not include monitoring of vitamin D levels, which is an unfortunate oversight because deficiency is easily treated. A previous study has shown that prenatal supplements that con-

tain 400 IU of vitamin D are not adequate to achieve normal vitamin D levels in pregnant women or their infants. Studies in pregnant women are under way in the United States with the use of vitamin D at doses of 2000 IU and 4000 IU daily to establish vitamin D recommendations during pregnancy.

Comment

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).

CLINICAL IMPLICATIONS

- *Vitamin D deficiency* is defined as serum 25(OH)D levels \leq 32 ng/mL.
- Vitamin D deficiency is estimated to occur in 5-50% of pregnant women; African American women have a much higher risk of vitamin D deficiency, compared with other US groups.
- Vitamin D deficiency is linked to increased prevalence of preeclampsia, low birthweight and size, and the development of childhood asthma and type 1 diabetes mellitus.
- 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. ■