

Vitamin D, Vitamin A, Maternal-Perinatal Considerations: Old Concepts, New Insights, New Questions

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Vitamins A and D are essential nutrients that play important roles in growth and development. Preterm and low birth weight infants have low levels of these nutrients and are at risk for developing detrimental health consequences associated with vitamin A and vitamin D deficiencies. Preliminary data suggest that vitamin A and D supplementation is needed to prevent deficiency. More work is needed to define optimal doses, timing, and modes of administration to ensure that an adequate supply of these vitamins is available to meet the critical needs during pregnancy and in high-risk neonates. (*J Pediatr* 2013;162:S26-30).

The fat-soluble vitamins A and D play important roles in perinatal growth and development. Maternal concentrations of these vitamins directly affect concentrations in the fetus and neonate. Preterm infants have low stores and are at risk for vitamin deficiency. Worldwide there is a silent epidemic of vitamin D deficiency. This is an important public health problem that not only relates to bone disease in the population, but also may increase the risk of developing a wide range of common chronic diseases in adult life. Although vitamin A deficiency is rarely seen in the US and other industrialized countries, it is a major nutritional concern in developing countries and is the leading cause of preventable childhood blindness.¹

Vitamin D

Definition and Functions

The term "vitamin D" refers to either vitamin D2 (ergocalciferol) or D3 (cholecalciferol). The major source of vitamin D3 is through the action of UV radiation from the sun on 7-dehydrocholesterol to form cholecalciferol in the dermal layers of the skin. Cholecalciferol is then enzymatically converted to 25-hydroxycholecalciferol [25(OH)D, or calcidiol]. The primary active form of vitamin D is 1,25-dihydroxycholecalciferol (calcitriol), which is formed from 25(OH)D by 1 α -hydroxylase. Final activation of calcitriol occurs in the kidneys and in many other tissues throughout the body. Calcitriol circulates bound to a vitamin D-binding protein to reach different organs. Calcitriol is also synthesized in or adjacent to regulated cellular targets, acting in an autocrine and paracrine fashion as well.²

Traditionally, the primary hormonal function of calcitriol is in controlling blood calcium concentrations by regulating the expression of genes involved in the intestinal absorption, renal excretion, and bone movement of this mineral. Many other functions of calcitriol have been identified as well, including immunomodulatory activity, insulin secretion, neuroprotective functions, and others.

Maternal Vitamin D Status

The best indicator of maternal vitamin D status is serum 25(OH)D concentration. New definitions of vitamin D sufficiency have evolved based on functional biomarkers, and an optimal 25(OH)D level has not yet been determined. The Institute of Medicine has recently proposed the following definitions³: (1) Sufficiency: 25(OH)D levels of at least 50 nmol/L (20 ng/mL); however, serum 25(OH)D concentrations >75 nmol/L (>30 ng/mL) are not consistently associated with increased benefit; (2) Risk of deficiency: serum 25(OH)D level <30 nmol/L (<12 ng/mL); and (3) Potential risk for inadequacy: serum 25(OH)D level 30-50 nmol/L (12-20 ng/mL).

Vitamin D deficiency is highly prevalent in pregnant and lactating women and produces adverse consequences in these women, their fetuses and, ultimately, their growing infants and children.^{4,5} Several factors are responsible for this epidemic, including increased awareness of the injuries associated with sun exposure, insufficient vitamin D intake, and the rising prevalence of obesity. Adult obesity is associated with low 25(OH)D levels; whether vitamin D insufficiency is a risk factor for increased body fat or body fat is a risk factor for vitamin D insufficiency is not well understood.⁶

25(OH)D	25-hydroxycholecalciferol
NbVAS	Newborn vitamin A supplementation
ROP	Retinopathy of prematurity
VLBW	Very low birth weight

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Data from the US National Health and Nutrition Examination Survey (2001-2006) revealed hypovitaminosis D (defined as a serum 25(OH)D level <50 nmol/L) in 80% of African American and 13% of white American women of reproductive age.⁵

Vitamin D deficiency is widely prevalent in pregnant women, and mothers with vitamin D deficiency remain deficient during lactation. In a study of American women at time of delivery, vitamin D deficiency [defined as 25(OH)D of <37.5 nmol/L] and insufficiency [defined as 25(OH)D of 37.5-80 nmol/L] were detected in 29.2% and 54.1% of black women, 45.6% and 46.8% of black neonates, 5.0% and 42.1% of white women, and 9.7% and 56.4% of white neonates. As recommended, 90% of mothers in the study had prenatal vitamin D intake of 400 IU/day.⁷ Similar results were reported in a study from northern India, where low levels of 25(OH)D (<22.5 ng/mL) were observed in >80% of women and >95% of infants.⁸ These studies highlight the high prevalence of vitamin D deficiency in pregnant women and their neonates.

Maternal Consequences of Vitamin D Deficiency during Pregnancy

Vitamin D deficiency has been linked to bone disease (ie, rickets and osteomalacia). In malnourished populations, osteomalacia in mothers and abnormal skeletal metabolism in fetuses and infants have been reported.⁹ Nonclassical consequences of vitamin D deficiency have been detected in pregnant women; experimental and observational studies have suggested that vitamin D deficiency may be associated with increased risk of preeclampsia, insulin resistance, and gestational diabetes.^{10,11} Whether this association suggests causality cannot be determined based on the available data.

Maternal Vitamin D Status and the Fetus

There is a strong relationship between maternal and fetal (cord blood) 25(OH)D concentrations. 25(OH)D readily crosses the placenta and is metabolized to 1,25-dihydroxycholecalciferol by the fetal kidney as early as 24 weeks' gestation. At birth, neonatal serum 25(OH)D concentration is 50%-70% of maternal serum 25(OH)D concentration.¹² The significance of maternal deficiency during pregnancy is that the fetus develops in a state of hypovitaminosis D, which likely has short-term and long-term detrimental effects.

Vitamin D deficiency in newborns is associated with hypocalcemia and osteopenia, especially in preterm infants. These effects on bone are long-lasting. In a longitudinal study of 198 children followed up at age 9 years, Javaid et al¹³ concluded that low maternal vitamin D concentration during the third trimester of gestation was associated with reduced whole-body and lumbar spine bone mineral content.

Different studies have suggested that vitamin D deficiency also may be associated with an increased risk of nonbone diseases and/or abnormal development in the fetus. Vitamin D has critical functions that affect organs other than bone. Vitamin D receptors and 1- α hydroxylase have been detected in the developing brain. Calcitriol target gene prod-

ucts, including neurotrophins NGF, NT3, and NT4/5, which are critical for neurogenesis, have been identified.² Epidemiologic data have confirmed associations between schizophrenia and winter birth and northern latitudes, which might result from low 25(OH)D levels.¹⁴ It remains to be seen whether vitamin D deficiency can be shown to negatively impact cognitive or behavioral endpoints in experimental or epidemiologic studies.

Whether vitamin D deficiency in infants is associated with long-term risk of diabetes should be considered as well. A retrospective study of a birth cohort of 10 366 children suggested that postnatal vitamin D supplementation (2000 IU/day) was associated with an 8-fold reduction in the incidence of type 1 diabetes mellitus.¹⁵ More studies are needed to analyze the role of hypovitaminosis D in the development of this public health problem.

Vitamin D deficiency also has been associated with an increased risk of autoimmune diseases, such as rheumatoid arthritis, allergy, multiple sclerosis, type 1 diabetes, and certain cancers.¹³ Evidence of causal relationships between vitamin D status and a disease or health outcome other than bone health remains elusive, however, owing to the multifactorial etiology of chronic diseases and the difficulty of isolating the effects of a single nutrient from other confounding effects.

Interventions to Improve Vitamin D in Pregnant Women

Although vitamin D supplementation is effective in preventing vitamin D deficiency, the optimal vitamin D requirement in women remains unknown. Studies evaluating plasma vitamin D status have shown that vitamin D supplementation of <2000 IU/day is not effective in achieving sufficiency.¹⁶ The standard recommended daily allowance for vitamin D supplementation in adults is 400 IU/day; the same dose is recommended during pregnancy. However, studies in adults suggest that a daily dietary allowance of 1000-2000 IU/day is needed to achieve a target circulating 25(OH)D value of at least 75 nmol/L.¹⁷ In another study of lactating women, intake of 6400 IU/day postpartum resulted in significantly higher levels of circulating vitamin D compared with controls.¹⁸ Higher amounts of vitamin D may be necessary, although the precise dose needed remains unknown.

Previous studies have explored the role of vitamin D supplementation on perinatal outcomes. A study of 23 423 nulliparous Norwegian pregnant women found a 27% reduction in the risk of preeclampsia in women receiving 10-15 μ g/day (600-800 IU/day) of vitamin D compared with women receiving no supplements.¹⁹ Another study suggested that vitamin D supplementation during pregnancy improved neonatal birth weight.²⁰

There is an urgent need to determine the optimal dose of vitamin D to maintain vitamin D sufficiency in pregnant women when sun exposure is inadequate or skin color limits the amount of vitamin D formed from UV radiation. Vitamin D deficiency during pregnancy not only may impair

maternal and fetal skeletal formation, but also may play a role in epigenetic “imprinting” that can affect other, extra-skeletal functions later in life and even influence reproductive outcomes.

Vitamin A

Functions

Vitamin A is involved in regulating and promoting growth and cell differentiation and in maintaining the integrity of respiratory epithelial cells. Vitamin A is also part of the photosensitive visual pigment complex in the retina and plays a role in reproductive functions and immunocompetence. Carotenoids, dietary precursors of vitamin A, have potent antioxidant properties.²¹

Prenatal Considerations

The mechanism of vitamin A transport across the placenta and its regulation are not fully understood. The estimated ratio of maternal to fetal plasma vitamin A concentrations in healthy pregnancies is roughly 2:1.²²

Trials in women of reproductive age conducted in countries with a high prevalence of vitamin A deficiency have reported conflicting results in relation to outcomes associated with vitamin A supplementation. A study in Nepal found that supplementation with vitamin A or its precursor (β carotene) in women of reproductive age reduced pregnancy-related mortality by 44% (95% CI, 16%-63%).²³ In contrast, a large-scale, randomized study performed in Ghana with more than 200 000 women of reproductive age found no improvement in perinatal or infant survival with vitamin A supplementation.²⁴ The different outcomes in these two studies may be related to the higher incidence of severe vitamin A deficiency in Nepalese women, as manifested by eye disease, compared with Ghanaian women. Large studies are needed to examine the role of vitamin A supplementation on reproductive outcomes.

It is important to emphasize that an oversupply of vitamin A can be toxic. Excess retinoic acid in the first trimester of pregnancy is reportedly teratogenic, leading to spontaneous abortions and fetal malformations, including microcephaly and cardiac anomalies.²⁵

Postnatal Considerations: Prematurity and Vitamin A

An “adequate” concentration of plasma vitamin A in very low birth weight (VLBW) infants has not yet been defined. Plasma concentration is not necessarily a good index of vitamin A status. Plasma concentrations can be normal even when tissue (liver, lungs, and other organs) stores are low. Nonetheless, a concentration $<200 \mu\text{g/L}$ ($0.70 \mu\text{mol/L}$) is considered deficient, and a concentration $<100 \mu\text{g/L}$ ($0.35 \mu\text{mol/L}$) indicates severe deficiency and depleted liver stores.¹

Preterm infants have lower plasma concentrations of retinol and retinol-binding protein compared with their term counterparts. This deficit is more severe in smaller babies, thus, in a multicenter study in extremely low birth weight

infants, 54% of extremely low birth weight infants who did not receive intramuscular vitamin A had a plasma retinol concentration $<0.70 \text{ mmol/L}$ at 28 days.²⁶

Role in Lung Development

Vitamin A is required in the fetal lung for cellular differentiation and surfactant synthesis. Vitamin A and steroid hormones have similar effects on prenatal and postnatal lung development, operate through similar cell receptors, and may be interdependent.

Administration of antenatal steroids may contribute to higher plasma vitamin A values measured soon after birth in the most immature preterm infants. In addition, postmortem studies have found larger lung and hepatic vitamin A stores in extremely low birth weight infants who received steroids. Indeed, the beneficial pulmonary response to steroids may be mediated in part by vitamin A. Werkman et al²⁷ reported a higher retinol:retinol-binding protein, reflecting poorer vitamin A status, in preterm infants who later developed bronchopulmonary dysplasia compared with those who did not.

Results from a meta-analysis of 8 eligible trials suggested that supplementation with vitamin A in VLBW infants was beneficial in reducing the combined effect of death or oxygen requirement at age 1 month. Three studies reported outcomes at 36 weeks' gestational age and showed a lower need for oxygen in infants who received vitamin A supplements. This beneficial outcome was observed only in infants with a birth weight $<1000 \text{ g}$.²⁸

The lungs of the preterm infant may be deficient in vitamin A at birth, but whether this can be modified by supplementation of either the mother or newborn infant is unknown. How lung concentrations of vitamin A relate (if at all) to plasma retinol is unclear. It is unknown whether providing the mother vitamin A in late pregnancy can decrease the risk of bronchopulmonary dysplasia and/or respiratory distress syndrome in newborns, or act as an effective adjunct to postnatal preventive therapy for respiratory morbidities.

Role in Visual Development

Low plasma vitamin A concentrations in preterm infants have been associated with the development of retinopathy of prematurity (ROP). However, there is insufficient evidence to support routine vitamin A supplementation to prevent ROP in preterm infants.²⁸ Additional studies are needed to define whether vitamin A supplementation might be beneficial in preventing ROP in preterm infants and, if so, to establish the optimum dosing and timing of supplementation.

Immune Function and Vitamin A

There is an urgent need for vitamin A supplementation to improve survival from infectious diseases in children in countries where vitamin A deficiency is prevalent. In these settings, the World Health Organization recommends periodic vitamin A supplementation in infants aged 6-59 months.²⁹ Routine newborn vitamin A supplementation (NbVAS) has yielded controversial results, however. In

Indian children, administration of NbVAS (24 000 IU on days 1 and 2) reduced infant mortality at 6 months by almost 25%, with the greatest effect observed in infants with low birth weight. The prevalence of severe diarrhea and septicemia was lower in the infants who received vitamin A.³⁰ In a study performed in Indonesia, a single dose of 50 000 IU given orally to term infants at birth reduced infant mortality at age 1 year by 64%. In contrast to the Indian study, the greatest impact was observed in infants with birth weight >2500 g; the prevalence of severe respiratory infections compared with placebo was also lower.³¹ Other studies have not confirmed these encouraging results, however, and systematic analyses of several trials have not documented any benefit from NbVAS.³² Thus, at present, the World Health Organization does not recommend routine NbVAS to reduce infant morbidity or mortality as a public health intervention.³³ More studies are needed to explore vitamin A status and neonatal outcomes in infants who receive vitamin A supplementation. Discrepancies among studies could be related to differences in the prevalence and severity of maternal vitamin A deficiency, in the timing and mode of vitamin A administration, in the dose of vitamin A administered, or other as yet unexplored reasons.

Role of Vitamin A in VLBW Infants

There is a need to further analyze the role of vitamin A supplementation in decreasing the incidence and severity of infectious diseases in sick VLBW infants. Pooled data from 2 studies (n = 807) in VLBW infants who received intramuscular vitamin A supplementation showed a nonsignificant trend towards a reduced prevalence of sepsis in these infants (typical risk ratio, 0.89; 95% CI, 0.76-1.05).³¹ Trials to specifically address this issue are still needed. In VLBW infants, the best results from vitamin A supplementation reported to date have been with intramuscular administration. One trial compared different intramuscular dosing regimens (5000 IU 3 times weekly for 4 weeks, 10 000 IU 3 times weekly for 4 weeks, or 15 000 IU weekly for 4 weeks) in infants weighing <1000 g. The optimal dose appeared to be 5000 IU 3 times weekly for 4 weeks; however, even with this dose, more than 25% of the infants had evidence of vitamin A deficiency.^{33,34} Higher doses or a better mode of delivery may be needed. Other routes of administration have proven less effective. Vitamin A administered intravenously degrades in light and adheres to tubing. Administration via the enteral route also is not optimal. Administration by inhalation appears feasible, but more study is needed.

In the future, it will be helpful to understand whether combining antenatal vitamin A supplementation of the mother with postnatal supplementation of the newborn can better prevent neonatal morbidity compared with postnatal supplementation alone. Moreover, it will be important to define whether vitamin A supplementation in lactating women improves vitamin A status in their infants and, if so, to identify the optimal dosage for this effect. For these approaches to be effective, it will be necessary to identify appropriate bio-

markers for vitamin A concentrations at the sites where biologically active vitamin A is stored.

Conclusion

Vitamin D deficiency is a worldwide public health problem that can affect pregnant women and their children. Hypovitaminosis D has acute and long-term negative effects on bone health, and growing evidence suggests a possible association with chronic disorders and adverse reproductive outcomes. Many gaps remain in the knowledge of vitamin D's modes of action, requirements, and appropriate levels.

Vitamin A deficiency is prevalent in developing countries. This nutrient is essential for normal development of the eye and immune system and apparently plays a role in lung function and maturation that is particularly important in preterm infants. Questions remain related to appropriate measures of sufficiency and optimum dosages to promote health in pregnant women and preterm and term infants. Research to address these questions is urgently needed. ■

Author Disclosures

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