Vitamin D Requirements during Infancy

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Introduction

Pregnancy and lactation represent unique time periods in human development where the health and nutritional status of one individual, the mother, directly impacts another, the fetus or infant. Expanding knowledge about vitamin D during these time periods has illuminated the role of vitamin D on maternal and infant bone health, cardiovascular health, immune function, and glucose metabolism. Despite these findings, studies continue to report extensive vitamin D insufficiency and deficiency during pregnancy and lactation that particularly affect women and their offspring who are of darker pigmentation, living at higher latitudes, and in the winter season. Caution must be taken with experimentation during these critical periods of human development, but also must proceed expeditiously as available research indicates long term health consequences of continued vitamin D insufficiency and deficiency.

Historical Perspective

Historical writings of bony deformities resembling rickets date back as far as the first century Greek and Roman writings but the definitive description emerged in the mid 17th century (1-3). In 1645, an English medical student by the name of Daniel Whistler first published a description of the disease, which was rampant in southwest England (1-3). In 1650, Francis Gliszen published a more scientific report on rickets, which remains a classic historic resource on the disease (1-4). The following two centuries led to little advancement in the understanding or treatment of rickets (5). By the early 20th century, rickets was epidemic in the northern, industrialized regions of the United States and Europe with 96 percent of infants demonstrating microscopic findings of the disease at autopsy (5,6). In 1919, Edward Mellanby conducted the first experiment designed to find the underlying cause and possible treatment of rickets (7,8). Through experimentation with puppies, Mellanby declared a clear role for diet in the etiology of rickets (8). Elmer McCollum and his colleagues at Johns Hopkins University can be credited with determining the nutritional factor deficient in diets leading to rickets, then named vitamin D (7,9,10).

Recognition of the role of sunlight in the development of rickets dates back to the mid 1800s with reports of lack of sunlight and poor diet leading the rickets (5). In 1890, Palm—a European researcher, noted that despite a superior diet and sanitary living conditions, infants living in Britain had an increased incidence of rickets when compared to infants living in the tropics (11). He, then recommended sun-baths for prevention and treatment of rickets (11). Finally in the 1920s, Park (12) and Harriette Chick and her coworkers (13) were able to confirm the use of cod liver oil (vitamin D) supplementation and sun exposure for the prevention and treatment of rickets. By the 1930s, routine vitamin D supplementation, sun exposure, and milk fortification in the United States led to an eradication of rickets (12,14).

Unfortunately, nutritional rickets reemerged in the 1980s, particularly among the African American and other darker pigmented populations. The recurring thread amongst the reported cases is that the infants are darkly pigmented, often living at higher latitudes, and are exclusively breastfed without vitamin D supplementation beyond six months of age (15). This finding led to a revised American Academy of Pediatrics (AAP) statement in 2003 recommending 200 IU of vitamin D supplementation to all infants receiving less than 500 ml of fortified formula per day to begin within the first two months of life (16). Continued reports of rickets, limited dietary sources of vitamin D, inadequate sun exposure for vitamin D synthesis, and an enhanced understanding of vitamin D physiology and its actions have led to the most recent revision of the AAP statement in 2008. The current recommendations are for all infants and children to be supplemented with a minimum of 400 IU per day of vitamin D beginning in the first few days of life (17).

Vitamin in Pregnancy

It had been known for decades that maternal vitamin D concentration largely determines the vitamin D status of the developing fetus and neonate. Despite this observation, the Institute of Medicine in 1997 (18) and a Cochrane Review in 2002 (19) concluded that little data exist regarding maternal vitamin D supplementation during pregnancy. During pregnancy, a woman needs vitamin D not only to maintain her health status, but also that of the placenta and developing fetus.

Adult vitamin D deficiency is widespread. Recent data indicates that an ideal level for 25(OH)D is greater than 40 ng/mL or 100 nmol/L (20). The first report of widespread vitamin D deficiency in women of child bearing age came from the United States Center for Disease Control (CDC) NHANES III report revealing that 42 percent of African American women had 25(OH)D levels below 15 ng/mL or 37.5 nmol/L (21), and more recent data in a large cohort in SC suggests this prevalence is around 75 percent (22).

A long standing unawareness of the short and long term health consequences of vitamin D insufficiency has led to widespread insufficiencies in most populations. A representation of the prevalence of vitamin D insufficiency around the world is as follows: 8 percent in Western women in the Netherlands (23), 18 percent in the United Kingdom (24), 25 percent in the United Arab Emirates (25), 42 percent in Northern India (26), 46 percent in Canada (27), 50 percent in non-European ethnic minority women in South Wales (28), 59-84 percent in women with darker pigmentation in the Netherlands (23), 61 percent in New Zealand (29), 71 percent in Pakistani women in Norway (30), and 80 percent in Iran (31).

A recent focus on fetal origin of adult dis-
ease has led to investigation of the exposure to vitamin D insufficiency during fetal development and its relationship to later disease processes. Specifically, there is growing evidence of vitamin D's effect in utero on fetal bone (32,33); later risk for schizophrenia (34-39), multiple sclerosis (40,41), childhood and adult cancers (42,43), autoimmune diseases and inflammatory disease states such as lupus (44), rheumatoid arthritis (45), and diabetes (46,47); concern about maternal and early infant vitamin D status is justified (1,48,49). Other support for the effect of vitamin D during fetal development comes from the work of Zimmermann, et al. (50), who showed a significant correlation between IL-10 (anti-inflammatory cytokine) and 25(OH)D status at birth. In addition to effects on the fetus, an article published by Bodnar in 2007 proposes that vitamin D deficiency may act as an independent risk factor for maternal preclampsia (a form of toxemia of pregnancy; a condition that may develop during pregnancy leading to severely elevated blood pressure, large amounts of protein in the urine, and can progress to seizures) (51). It is becoming increasingly clear that adequate maternal vitamin D status is essential not only to maternal well being but also to fetal development during pregnancy. Obstetrical healthcare providers should consider assessing maternal vitamin D status by measuring serum 25-OH-D levels in pregnant patients. If found to be insufficient, a mother should be supplemented with vitamin D3 to reach sufficient 25-OH-D concentrations (greater than 32 ng/mL or 80 nmol/L) (52-56).

Vitamin D and Human Milk

The natural progression from placental nutrition during pregnancy is human milk provided after delivery (57). Human milk is considered the ideal nutrition for the neonate and growing infant with one caveat— it lacks sufficient concentrations of one essential vitamin— vitamin D (16). Without adequate vitamin D supplementation, the infant is at risk for developing rickets, a disease most often associated with exclusive breastfeeding.

One may wonder why the ideal infant nutrition would be deficient in an essential vitamin for normal human development. Over the centuries, society has changed from one with significant sun exposure allowing synthesis of maternal vitamin D in the skin to one in which people remain indoors or block the sun with clothing, lotions, and hats to avoid the possibility of sun damage. Unfortunately, this has resulted in widespread maternal vitamin D deficiency. With lactating mothers having inadequate stores of vitamin D for themselves or their infants, vitamin D deficient human milk ensues.

Even with maternal supplementation of recommended daily intake of 400 IU per day of vitamin D3, human milk contains only 33-68 IU/L, far below the required 200-800 IU per day to prevent rickets (58-61). With an evolving understanding of vitamin D sufficiency and vitamin D toxicity and the advent of higher doses for supplementation of vitamin D to achieve sufficiency in adults, the concept of maternal supplementation to achieve infant vitamin D sufficiency has developed. Ongoing investigations to determine a safe yet effective vitamin D dose to maintain maternal and infant vitamin D sufficiency are underway (62). Prior investigations have demonstrated the ability to improve vitamin D concentration in human milk through exposure to UVB radiation as well as through maternal supplementation (58,59,61,63).

Vitamin D and Lactation

Vitamin D Supplementation of the Breastfeeding Infant

In 2003, in accordance with the National Academy of Sciences recommendations, the AAP reduced its previous recommendation for 400 IU of vitamin D per day for infants to supplementation of 200 IU of vitamin D per day to all breastfed infants in the first 2 months of life, at a time when breastfeeding was well established (16). This was in agreement with a 1997 report from the Institute of Medicine as well (18). The change was based principally on data from the United States, Norway, and China showing that 200 IU of vitamin D would prevent physical signs of vitamin D deficiency as well as maintain 25-OH-D levels in the sufficient range, greater than or equal to 11 ng/mL or 27.5 nmol/L (16). Research has shown that breastfed infants can maintain sufficient vitamin D status solely through adequate sunlight exposure (76,77); however, concerns regarding the future development of skin cancers and subsequent application of sunscreen and protective barriers makes adequate sun exposure for vitamin D synthesis unlikely in most infants (17,78).

Since the implementation of the AAP recommendations in 2003 (79), there has been increased information in adults linking vitamin D insufficiency to other biochemical markers involved in bone mineralization, calcium absorption, insulin resistance, and the function of the immune system (17,80,81). As a result, concerns have arisen regarding the adequacy of supplementation with only 200 IU of vitamin D (D). See table 2). In fact, in response to these findings, new definitions of vitamin D deficiency and insufficiency have developed. For adults, vitamin D deficiency is now defined as a 25-OHD level less than 20 ng/mL or 50 nmol/L, and vitamin D insufficiency as a 25-OHD level in the range of 20 ng/mL to 30 ng/mL 50

![Table 1. Contemporary Clinical Trials of Vitamin D Supplementation during Lactation](image)

<table>
<thead>
<tr>
<th>Maternal vitamin D supplementation</th>
<th>Infant vitamin supplementation</th>
<th>Maternal 25(OH)D (ng/ml)</th>
<th>Milk Antithrombin Activity (%)</th>
<th>Infant 25(OH)D (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,000 IU/day</td>
<td>0</td>
<td>36.1</td>
<td>69.2</td>
<td>27.8</td>
</tr>
<tr>
<td>4,000 IU/day</td>
<td>0</td>
<td>44.5</td>
<td>134.6</td>
<td>30.8</td>
</tr>
<tr>
<td>6,400 IU/day</td>
<td>0</td>
<td>58.8</td>
<td>97.3</td>
<td>46</td>
</tr>
<tr>
<td>400 IU/day</td>
<td>300 IU/day</td>
<td>38.4</td>
<td>45.6-78.6</td>
<td>45</td>
</tr>
</tbody>
</table>

vitamin D is inadequate to achieve 25-OH-D sufficiency is defined as a 25-OH-D level of greater than 32 ng/mL or 80 nmol/L.

Definitive ranges for infants and children have yet to be declared, but research has shown that supplementation with 200 IU per day of vitamin D is inadequate to achieve 25-OH-D levels greater than 20 ng/mL or 50 nmol/L. While supplementation with 400 IU per day of vitamin D is adequate to achieve 25-OH-D levels of at least 20 ng/mL or 50 nmol/L (17, 59, 82). This premise is based on the following well-established facts:

1. Vitamin D deficiency can occur early in life, particularly when many pregnant women themselves are deficient.
2. 25-OH-D levels of unsupplemented breastfed infants are often below 20 ng/mL or 50 nmol/L, particularly in winter months and latitudes farther from the equator, probably as a result of maternal deficiency.
3. Adequate sunlight exposure in a given infant to achieve adequate vitamin D synthesis is difficult to determine and often not achieved.
4. 25-OH-D levels can be maintained greater than 20 ng/mL or 50 nmol/L in breastfed infants with vitamin D supplementation of 400 IU per day of vitamin D (17).

In light of these observations, the AAP recently amended its previous recommendation for vitamin D supplementation of infants and children (17). The current recommendation reads, "A supplement of 400 IU/day of vitamin D should begin within the first few days of life and continue throughout childhood. Any breastfeeding infant, regardless of whether he or she is being supplemented with formula, should be supplemented with 400 IU of vitamin D." Vitamin D preparations either in vitamin D-only or multi-vitamin supplements are readily available and inexpensive. (See table 3.)

As human milk has repeatedly been reaffirmed as the ideal nutrition for infants' healthy growth and development with the exception of inadequate concentrations of vitamin D, the ideal situation would be to improve the nutritional status of the human milk to avoid the need for any supplementation. Early investigation to improve maternal vitamin D status, thereby improving the nutritional status of a mother's milk, is promising, but a well-established dose to achieve this goal has not yet been determined. In addition, we know that vitamin D insufficiency affects multiple organ systems including the immune system, bone mineralization, and the cardiovascular system based upon adult literature, but the long-term implications for fetuses and infants developing in a vitamin insufficient state have not been studied. A current area of interest is the fetal origin of adult disease. How does vitamin D insufficiency and frank deficiency during early development of an embryo and into infancy impact the innate programing for adult disease? In order to answer these questions further research is needed, particularly in the areas of vitamin D in relation to pregnancy, lactation, and long-term consequences for the infant.

### Table 2. Vitamin D Deficiency

<table>
<thead>
<tr>
<th>Clinical Signs and Stages of Vitamin D Deficiency</th>
<th>Stage 1</th>
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</thead>
<tbody>
<tr>
<td>1. Decreased absorption of intestinal calcium, urinary loss of phosphorus; normal calcium levels maintained</td>
<td></td>
</tr>
<tr>
<td>2. Bone demineralization to maintain normal serum calcium levels</td>
<td>Stage 2</td>
</tr>
<tr>
<td>3. Decreased levels of calcium and phosphorus in the blood</td>
<td>Stage 3</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Disease States Associated with Vitamin D Deficiency</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1. Autoimmune Diseases (through Vitamin D's actions on the innate immune system)</td>
<td></td>
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<tr>
<td>• Rheumatoid Arthritis</td>
<td></td>
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<tr>
<td>• Systemic Lupus Erythematosus</td>
<td></td>
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<tr>
<td>• Multiple Sclerosis</td>
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<tr>
<td>• Diabetes Mellitus, Type I</td>
<td></td>
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<tr>
<td>• Crohn's Disease</td>
<td></td>
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<tr>
<td>2. Cancer</td>
<td></td>
</tr>
<tr>
<td>• Head and Neck</td>
<td></td>
</tr>
<tr>
<td>• Breast</td>
<td></td>
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<tr>
<td>• Prostate</td>
<td></td>
</tr>
<tr>
<td>• Colon</td>
<td></td>
</tr>
<tr>
<td>3. Cardiovascular Disease (through inflammation)</td>
<td></td>
</tr>
<tr>
<td>4. Alteration in Mobility</td>
<td></td>
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<tr>
<td>5. Insulin resistance</td>
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</tbody>
</table>

Adapted from AAP Vitamin D Statement, Table 1 (17, 80, 81).

### Conclusion

As a result of inadequate nutritional vitamin D intake and global concerns regarding sun exposure as well as changes in the definition of vitamin D sufficiency, vitamin D deficiency and insufficiency have become commonplace. Of utmost importance to our field of medicine is the incidence of vitamin D deficiency during pregnancy and lactation, which then impacts the fetus and newborn. Literature clearly supports supplementation of pregnant women to improve their health status as well as that of their developing fetus. Although supplementation of a lactating mother should be recommended for her health benefits, the dose at which supplementation of the mother would also benefit the breastfeeding infant has yet to be clearly defined. Therefore, at this time, supplementation of the breastfeeding infant with 400 IU of vitamin D per day should continue to be recommended.

### References

18. Standing Committee on the Scientific Evaluation of...


Figure 1. Photochemical Pathway of Vitamin D Synthesis Dependent on the SUN

7 - Dehydrocholesterol in Epidermis of Skin

Previtamin D$_3$ forms when UVB hits 7-dehydrocholesterol

Heat from skin converts to Vitamin D$_3$

Vitamin D$_3$ enters Bloodstream

25-hydroxyvitamin D$_2$ and D$_3$ [25(OH)D]

25-hydroxylase

Extrarrenal conversion of 25-hydroxyvitamin D to active metabolite 1,25-dihydroxyvitamin D

Calcin absorption (small intestine)

Urinary calcium reabsorption (kidney)

Bone mineralization

Effects on innate immune system

1,25-dihydroxyvitamin D [1,28(OH)D]

Vitamin D Synthesis

Dependent on the SUN

Minor Sources: Dietary Vitamin D$_2$ - plants/supplements

Vitamin D$_3$ - animal source such as fish and fortified foods

7-dehydrocholesterol

Heat from skin converts to Vitamin D$_3$

Previtamin D$_3$ forms when UVB hits 7-dehydrocholesterol

Calcium absorption (small intestine)

Urinary calcium reabsorption (kidney)

Bone mineralization

Effects on innate immune system

1,25-dihydroxyvitamin D [1,28(OH)D]

Editor's Note: Dr. Carol Wagner presented at the LLLI 2008 Physicians Seminar on the topic of vitamin D. She graciously indicated that she would continue to be available to advise LLLI on this topic and also helped to write the fall 2008 LLLI media release. Dr. Wagner will be speaking on this topic on Thursday, July 9, 2009, as part of the EUS Healthcare Provider Seminar and Kaleidoscope Training Symposium at the Philadelphia Airport Hilton (PA, USA). For more information, contact dbuier@lllei.org or rharris@lllei.org.

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