Vitamin D in Preterm and Full-Term Infants

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Key Messages
• Dietary vitamin D intake should be assured in all infants, preterm and full term, with emphasis on adequate supplementation of infants who are receiving human milk.
• Usual total dietary intake level should be approximately 400 IU daily in healthy infants.
• There are multiple methods for providing vitamin D to infants; these may be selected based on parental desires.

Keywords
Bone health · Calcium absorption · Vitamins

Abstract
Vitamin D is necessary for the active (transcellular) absorption of calcium and for skeletal health. Inadequate vitamin D in infants leads to increased risks of poor bone mineralization and ultimately rickets. Rickets is uncommon in full-term infants with a much higher risk in very premature infants. However, the primary cause of rickets in premature infants is a deficiency of calcium and phosphorus, not vitamin D. Available research, as well as most guidelines, recommend an intake of 400 IU daily of vitamin D as adequate for bone health in preterm and full-term infants. Higher doses have not been consistently shown to have specific clinical benefits for healthy infants. There are no strong data to support either routine testing of serum 25-hydroxyvitamin D or targeting high serum 25-hydroxyvitamin D levels (e.g., 30 ng/mL) in healthy preterm or full-term infants. Vitamin D is commonly provided to infants via drops for breastfed babies or via infant formula, although alternative dosing approaches exist for breastfed infants, which some families may prefer. These include the use of drops placed on the mother’s breast, dissolvable doses, and high maternal doses (approximately 6,400 IU daily). Infant formula contains vitamin D, and most infants will reach an intake from formula of about 400 IU daily within the first 2 months of life if they are consuming routine cow milk-based formula. Although vitamin D toxicity is very uncommon, caution should be used to avoid extremely concentrated high doses found in some commercially available drops. Infants with liver or kidney disease may need special attention to vitamin D intake and status. Further research is needed to define the role of vitamin D in non-bone health outcomes of infants and to identify methods to enhance compliance with current recommendations for vitamin D intake in infants.
Vitamin D Physiology and Bone Health in Infants

Vitamin D is an essential nutrient for bone health in all individuals, including infants regardless of size or gestational maturity. Although other roles for vitamin D in health and disease exist, this discussion will focus on bone health, especially bone health in infants who do not have underlying endocrine disorders or severe nutritional diseases.

Vitamin D is critical for the transcellular absorption of calcium, via its active form, 1,25 dihydroxyvitamin D. Dietary vitamin D or vitamin D formed via solar exposure is converted in the liver to the circulating and primary storage, 25-hydroxyvitamin D (25(OH)D). The 25(OH)D is then transferred to the kidney where it is converted to 1,25 dihydroxyvitamin D. These physiological processes function normally in preterm and full-term infants who are otherwise healthy. A detailed review of vitamin D-related physiology can be found elsewhere [1].

Serum 25(OH)D in Infants

The role of serum 25(OH)D as a marker of vitamin D status has been extensively reviewed and discussed in a 2011 Institute of Medicine (IOM) report [2]. There are no recommendations either in that report or in any official American Academy of Pediatrics (AAP) statement for routine screening of 25(OH)D level in healthy preterm or full-term infants [2–7]. It is critical to understand that 25(OH)D is not necessarily a marker of physiological vitamin D function as it is not the primary active form of vitamin D. Rather, its concentration in the serum is valuable as a means of assessing individual and population vitamin D status. Different values for serum 25(OH)D have been described as “inadequate” or “deficient” in the literature. However, the adequate serum level indicated by the IOM and subsequently affirmed by the AAP of at least 20 ng/mL is the value that may be used for infants, both preterm and full term [2–6], pending further information clearly documenting nonbone health-related benefits to higher minimum levels. There are no data reliably establishing a value of 25(OH)D that is toxic, especially in infants. Values of >100 ng/mL have been used to indicate toxicity without good clinical correlation of this or any specific toxic 25(OH)D level [7]. Nonetheless, uncommonly, vitamin D toxicity associated with hypercalcemia can exist in infants and may cause significant illness.

Values of serum 25(OH)D in the range often considered “inadequate” (12–20 ng/mL) are not generally associated with clinical evidence of vitamin D deficiency causing inadequate calcium absorption or rickets in infants. Vitamin D-deficient rickets is commonly seen with values of serum 25(OH)D below 12 ng/mL, although this is dependent on calcium intake as well as vitamin D status. In adults, data have suggested that values of 12–20 ng/mL are associated with normal efficiency of vitamin D-dependent calcium absorption, but data in infants are very limited as such studies are difficult to perform [2, 8]. In older children, values above about 12 ng/mL are associated with adequate calcium absorption, although there is a small, likely clinically insignificant, benefit to calcium absorption associated with increasing values [9].

In considering rickets, it is the relationship between vitamin D and calcium intake and status, as well as the status of other minerals, especially phosphorus and magnesium, which are crucial for the development of rickets. Because of this central role of mineral deficiency, rickets is not accurately described as being entirely a disease of vitamin D deficiency in any group of infants, especially preterm ones. Furthermore, some rare disease states in which vitamin D function is not present are relatively effectively treated with high doses of oral calcium [10].

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Vitamin D Intake and Function

The relationship between dietary intake of vitamin D and serum 25(OH)D levels has been evaluated both in preterm and full-term infants for many years. There are far fewer data relating 25(OH)D levels and bone mineral content or density in preterm infants or even fracture rates in these infants. Some data suggest a possible benefit for higher 25(OH)D levels on bone mineralization but need confirmation in larger trials and correlation with clinical events and outcomes [11–13]. There are no data indicating that doses of vitamin D of 400 IU daily, or serum 25(OH)D achieved with those doses, are associated with an increased risk of rickets or fractures in any population of preterm or full-term infants.
Most data in infants, both preterm and full term, do not specifically allow for an understanding of the relationship between body weight and dose-response of vitamin D intake. The IOM report considered these relationships related to age but not specifically for infants [2]. Although cutaneous production of vitamin D exists in infants, this too is generally minimally considered in most research as it is extremely hard to quantify, and the use of sunblock as well as other factors limiting sun exposure make this an unreliable source of vitamin D for infants. Recommendations for vitamin D intake, including those of the IOM [2], are generally done on the assumption that cutaneous conversion of pro-vitamin D to vitamin D in infants is minimal or nonexistent.

Calcium absorption in all populations is both by transcellular vitamin D-dependent and by paracellular vitamin D-independent mechanisms. There are very few data to indicate the timing and relative role of these 2 mechanisms in newborns, whether preterm or full term. Numerous studies in preterm infants have shown a high level of calcium absorption, about 50% (compared to adults of 10–25% typically), in preterm infants. This includes infants fed human milk with or without fortification and those fed preterm formula across a broad range of calcium intakes [14, 15]. It has been suggested that these data indicate the likelihood that calcium absorption is primarily paracellular, not vitamin D dependent, in the first weeks of life in both preterm and possibly in full-term infants [16]. Transition to a greater proportion of calcium absorption by vitamin D-dependent active absorption may not occur for 1–2 months, but there are no data clearly defining this timing. Such research is nearly impossible to conduct, and we may never have a definitive answer to the timing and relative proportion of active versus passive calcium absorption in small infants and its relationship to dietary intake.

Preterm Infants

For preterm infants, it is generally found that a standard total intake of 400 IU daily will achieve a value of serum 25(OH)D above 20 ng/mL in most infants with averages well above 30 ng/mL [12] (Fig. 1). Some infants, especially those who have lower maternal vitamin D status at birth, may take longer to reach this value, but there are no suggestions of any clinical benefit to routinely giving higher doses [5]. A few infants receiving higher doses of vitamin D may have potentially toxic levels exceeding 100 ng/mL, but more information is needed.

**Fig. 1. Usual vitamin D intake in infants.**

![Usual vitamin D intake in infants](image-url)
to evaluate this risk or any clinical correlates of relatively high vitamin D status in preterm infants [12].

However, in this regard, there are differences in recommendations between those commonly given in the USA and in Europe for vitamin D in preterm infants. European authorities and authors have generally recommended a dose of 800–1,000 IU vitamin D daily, whereas in the USA, 400 IU daily remains the standard recommendation [17]. This distinction is due to the perspective in European reviewers, based on limited-balance studies, that a lower calcium intake can be used with a higher vitamin D intake to increase total calcium absorption to needed levels to support preterm infant bone mineralization. In the USA, it has been preferred to maintain a high calcium intake [4], and there are no current reasons to change recommendations or formulations of preterm infant products in the USA as there is no evidence of any harmful effects from calcium intake levels currently provided. Nonetheless, those who supplement preterm infants to a total intake of 800–1,000 IU daily may likely do so without serious concern for toxicity or need for close follow-up, given the long history of use of higher doses up to 1,000 IU daily in many countries in preterm infants.

### Dietary Sources of Vitamin D and Timing of Introduction

Because neonatal vitamin D status is reflective of maternal status, it has been suggested that it is best to start supplementation as early as is possible [2]. As such, whereas earlier recommendations in full-term infants suggested waiting until up to 6 weeks to allow lactation to become well-established, more recently, it is recommended that vitamin D be started within the first few weeks if not the first days of life.

One important reason for this is that it is easier and more reliably performed to teach families to properly give the drops to their breastfed infant while still in the hospital as it is less likely to be missed if begun in the hospital. In some hospitals,
the first bottle of the drops may be sent home with the family. The opportunity to rapidly increase very low 25(OH)D levels in infants born to mothers with very low levels is also a reason to consider this. However, it should not be expected that there will be specific clinical benefits to beginning vitamin D in the first weeks of life, and if some families wish to delay giving drops for 4–6 weeks until lactation is well-established that should be considered as reasonable.

The situation for preterm infants is even less clear. Rickets in preterm infants is primarily a disease of inadequate calcium and phosphorus intake and absorption. For those fed intravenously with parenteral nutrition, vitamin D is present in the multivitamins given with the parenteral nutrition with the standard intravenous multivitamin supplement containing 400 IU of vitamin D in 5 mL of the supplement. Typical dosing of 2 mL/kg daily of the supplement in parenteral nutrition would lead to doses from 160 to 400 IU daily for infants 1.0–2.5 kg. It is important to provide vitamin D to infants who are not taking enteral nutrition to prevent extremely low vitamin D levels which can increase bone resorption and cause failure to fully mineralize bone.

The timing of introduction of oral vitamin D in preterm infants has not been studied in terms of relative risks and benefits to any particular time point. The AAP recommended beginning after full feeds are achieved at about 1,500 g, but it was recognized that this specific time point is arbitrary and chosen primarily to ensure the tolerance of the drops. Others might choose to begin supplementation somewhat earlier in very-low-birth-weight infants, but it is common to ensure a nontrophic volume of feeds are being well tolerated before doing so and waiting until after parenteral nutrition has been discontinued.

Other Issues with Vitamin D Dosing in Infants

Some families are resistant to providing drops of vitamin D to their breastfed infants or perceive them to be poorly tolerated, especially when given with iron-containing multivitamins. In these cases, there are several alternatives that may be considered (Fig. 2). The first is the use of vitamin D drops that can be placed directly on the breast or given as dissolvable filmstrips.
For some mothers, this is easier and more acceptable than giving a dropper of vitamins directly to the infant or mixed in their milk [23].

Another approach is to have the lactating mother take a relatively high dose of vitamin D. Studies have shown that a maternal dose of 6,400 IU daily will provide an infant with adequate vitamin D intake (usually about 300–400 IU daily) from the mother’s milk if fully breastfed and if the mother takes the dose every day. Of note is that lower maternal doses, especially those of 400–2,000 IU daily, do not provide adequate vitamin D in breast milk. The dose of 6,400 IU daily is slightly above the IOM upper limit of 5,000 IU/day but is highly likely to be safe, and this should not be a concern in recommending this approach if desired by breastfeeding women [2, 24].

It is frequently asked whether vitamin D should be given to infants who are both breast and formula fed, and the general answer is “yes.” An intake of 400 IU daily requires a full volume of formula intake, and whereas going slightly below the 400 IU/day level of intake is not problematic, the mixed-fed baby is best served by providing additional vitamin D as would be done for fully breastfed infants. There is no risk of toxicity with this approach, even if the infant switches entirely to infant formula prior to stopping the vitamin D supplementation.

Another common clinical question is whether vitamin D supplementation via drops is necessary for exclusively formula-fed infants. Some have indicated that vitamin D should be given until a volume of formula intake of 1,000 mL/day is reached [7]. This is because, based on the formula label and usual dilution of powdered infant formula, vitamin D was usually provided in infant formulas at 400 IU/L. Although there is no harm in this practice, it is questionable if needed and if it is best use of family and societal resources. The vitamin D requirement of 400 IU daily from the IOM is an average requirement in the first 6 months of life and as noted, there is little suggestion of a clinical concern with slightly lower doses until full feeding volume is achieved [2].

Also problematic with this recommendation is the perception that 1,000 mL daily is the minimum volume of infant formula an infant should receive and infants taking below that need any supplements. The usual volume of breast milk intake is approximately 800 mL daily, and although formula intakes are somewhat variable, an intake of 1,000 mL of formula is higher than required for growth and development, and not all infants will ever take this volume nor should they be pushed to this volume [2]. Furthermore, although the label claim for vitamin D content was commonly 400 IU/L, when analyzed, many infant formula batches will have 10–20% over this amount so as to meet the label claim at the end of shelf life [25]. Overall, the IOM recommendation of 400 IU daily for infants should be understood as an average intake, not one needing to be met from label claim every day from birth [2].

Recently, many formulas have been marketed with vitamin D intakes over 400 IU/L as this is permitted by the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) [26]. Numerous routine cow milk-based and other formulas marketed currently contain approximately 400 IU in 800 mL as prepared, a daily intake volume similar to that ingested daily by many infants after the first 6–8 weeks of life (Table 2). Despite variations in the vitamin D content of infant formulas, there is no reason to specifically choose an infant formula based on vitamin D intake. Overall, there is no clinical evidence supporting routine supplementation of infants who are exclusively formula fed with vitamin D, and the emphasis should be on breastfed infants in this regard.

### Common Disease-Oriented Issues in Infants

#### Hypocalcemia

Most cases of neonatal hypocalcemia with symptoms are not primarily due to vitamin D deficiency. Both early and late hypocalcemia are common in preterm and term infants, and in

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**Table 2. Regulatory guidance and common vitamin D content of routine cow milk-based infant formulas**

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<tr>
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<th>Concentration, IU per 100 kcal</th>
<th>Approximate intake, IU daily&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>Europe (EFSA regulatory)</td>
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<td>100</td>
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<td>USA formulas (most common)</td>
<td>45</td>
<td>75</td>
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FDA, Food and Drug Administration; EFSA, European Food Safety Authority. <sup>a</sup> Based on 1,000 mL daily formula intake.
the USA, early hypocalcemia in preterm infants (first 2–3 days of life) is primarily related to hormonal factors [27, 28]. In full-term infants, hypocalcemia is commonly seen in infants of diabetic mothers or associated with severe birth depression and neonatal asphyxial disorders among other causes. In late hypocalcemic tetany (usually 4–7 days of age), vitamin D levels may be low, but the primary cause of hypocalcemia is the use of high phosphorus intakes associated with whole cow milk or use of infant formula [29, 30]. In late neonatal hypocalcemia, treatment with 1,25-dihydroxyvitamin D may shorten the time to resolution likely due to direct effects of vitamin D on the bone rather than a calcium absorptive effect [31].

An important situation in which vitamin D deficiency is more central to the etiology of hypocalcemia are cases commonly reported in full-term infants during the second week of life. Reports of this problem have primarily come from Middle Eastern countries and are associated with extremely low maternal and, thus, infant vitamin D levels [32, 33]. Although the etiology of the hypocalcemia is not clearly defined, likely it is due both to lack of effects of vitamin D at the bone and in the intestine. This highlights the importance of identifying at-risk maternal populations and providing them with adequate vitamin D intake during pregnancy.

Cholestasis
Common conditions related to the vitamin D requirement in preterm infants are those that affect either the enteral absorption of nutrients or those which affect the formation of 25(OH)D in the liver or 1,25-dihydroxyvitamin D in the kidneys. Absorption of fat-soluble vitamins, such as vitamin D, may be affected by a variety of disease states in preterm infants, including those with the loss of the terminal ileum surgically and malabsorptive diseases, such as cystic fibrosis. Management of these conditions is beyond the scope of this review, but these would be an indication for closely monitoring the serum 25(OH)D concentration and potentially providing higher doses of vitamin D or vitamin D metabolites as described below [34].

A second relatively common problem in high-risk neonates is cholestasis, especially secondary to long-term parenteral nutrition use. Although relatively little is known specifically about relating the level of conjugated bilirubin to 25(OH)D values or calcium absorption in infants, this may become a clinical problem in which it is difficult to maintain adequate vitamin D status using usual dietary approaches. In this case, if careful monitoring and higher vitamin D (e.g., 1,000–2,000 IU daily) intakes show a persistent level of serum 25(OH)D <20 ng/mL, then supplementation with very-high-dose vitamin D or use of vitamin D analogues, such as calcitriol, while continuing vitamin D may be considered [35]. This should generally be done in the context of consultation or management by a pediatric endocrinologist, nephrologist, or other expert in the use of vitamin D metabolites. Of note is that the enteral medication 25(OH)D, called calcidiol (also referred to as calcifediol), has recently become available in the USA but does not have a FDA-approved indication for use in infants and children.

Compliance with Vitamin D Intake Recommendations

As noted, many families of breastfed infants do not provide vitamin D supplements per recommendations. Recent data suggest that only about 20% of US infants who are breastfed are receiving vitamin D supplements to meet the recommendations [36]. Of note is that this is much lower than the rate in a study in Canada which found over 70% adherence, perhaps due to greater awareness of this issue in Canada among pediatricians and families [37]. Discharge from the hospital with vitamin D can markedly increase this rate as suggested in these preliminary results [38]. Education is needed for both providers and families related to the risks of rickets and the importance of providing vitamin D for infants. Providers should be prepared to answer concerns related to the use of drops in breastfed infants and provide alternatives as described above for those families unwilling to use drops. The option of delaying the drops for 6–8 weeks after birth can also be given, especially for families intending to offer a bottle of mother’s milk at that time into which the drops could be added.

Future Research

Further studies are needed focusing on the risks associated with very low vitamin D status in infants, in particular, identifying the risks and best management approaches for infants who are at risk of hypocalcemia from extremely low maternal vitamin D status. Although this problem has not been identified commonly in the USA, it may not be identified when it occurs, and population studies of high-risk maternal infant pairs are needed.

Although vitamin D is largely safe, the increasing use of high-dose supplements in infants should be evaluated and practitioners encouraged to report cases to understand this problem and the clinical consequence of high-dose ingestion, whether intentional or accidental.
Summary of Recommendations

Vitamin D is a critical nutrient for bone health and needs to be provided to all infants whether via infant formula or as a supplement to breastfed infants or high-dose supplement to their mothers. Solar conversion and cutaneous formation of vitamin D cannot be ensured in any population. In most healthy infants, preterm as well as full term, who are on full enteral nutrition and have a normal intestine and normal liver and renal function, provision of approximately 400 IU daily is necessary and sufficient for bone health, and routine monitoring of serum 25(OH)D levels is not needed. Caution should be used to ensure that the appropriate dose is provided and that accidental ingestion of high doses of vitamin D does not occur.

References


