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## **Calcium and Vitamin D Requirements of Enterally Fed Preterm Infants**

Steven A. Abrams and the COMMITTEE ON NUTRITION

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## CLINICAL REPORT

# Calcium and Vitamin D Requirements of Enterally Fed Preterm Infants

## abstract

FREE

Bone health is a critical concern in managing preterm infants. Key nutrients of importance are calcium, vitamin D, and phosphorus. Although human milk is critical for the health of preterm infants, it is low in these nutrients relative to the needs of the infants during growth. Strategies should be in place to fortify human milk for preterm infants with birth weight <1800 to 2000 g and to ensure adequate mineral intake during hospitalization and after hospital discharge. Biochemical monitoring of very low birth weight infants should be performed during their hospitalization. Vitamin D should be provided at 200 to 400 IU/day both during hospitalization and after discharge from the hospital. Infants with radiologic evidence of rickets should have efforts made to maximize calcium and phosphorus intake by using available commercial products and, if needed, direct supplementation with these minerals. *Pediatrics* 2013;131:e1676–e1683

In 2011, the Institute of Medicine (IOM) released dietary guidelines for calcium and vitamin D intakes for all age groups.<sup>1</sup> However, no intake recommendations were made specifically for preterm infants, because they were considered a special population and did not fit within the guidelines for dietary reference intakes developed by the IOM. Preterm infants have unique bone mineral requirements that may not be assumed to be similar to those of full-term newborn infants. Previous statements in the United States have limited their recommendations to full-term infants.<sup>2,3</sup> However, The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition has recently described enteral nutrition recommendations for preterm infants.<sup>4,5</sup>

Data on in utero bone mineralization rates are limited. Cadaver studies, beginning with the classic work of Widdowson et al,<sup>6</sup> generally support an in utero accretion of calcium during the third trimester of 100 to 130 mg/kg per day, peaking between 32 and 36 weeks' gestation. Phosphorus accretion is approximately half the accretion of calcium throughout gestation. Remarkably, more recent reevaluation of these data by using modern body composition techniques<sup>7</sup> provided values similar to those developed by Widdowson et al.<sup>6</sup>

In full-term infants, there is a strong correlation between maternal and infant cord blood 25-hydroxyvitamin D (25-OH-D) concentrations, although the cord blood concentration is less than the maternal concentration.<sup>8</sup> A substantial proportion of pregnant women, especially

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**KEY WORDS**

preterm infants, human milk, vitamin D, calcium, phosphorus, nutrient intake

**ABBREVIATIONS**

25-OH-D—25-hydroxyvitamin D

APA—alkaline phosphatase activity

IOM—Institute of Medicine

VLBW—very low birth weight

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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African American and Hispanic women in the United States and Europe, have 25-OH-D concentrations <20 ng/mL (50 nmol/L),<sup>9</sup> a value set for the basis of the Recommended Dietary Allowance.<sup>1</sup> However, in utero, skeletal mineralization is primarily independent of maternal vitamin D status, making the clinical significance of 25-OH-D concentrations during pregnancy unclear.<sup>10,11</sup>

### EFFECTS OF PRETERM BIRTH ON MINERAL METABOLISM

Population-based studies of rickets among preterm infants are lacking; therefore, the frequency is not known or reliably estimated. Approximately 10% to 20% of hospitalized infants with birth weight <1000 g have radiographically defined rickets (metaphyseal changes) despite current nutritional practices.<sup>12</sup> This frequency is much lower than the 50% incidence in this population described before fortification of human milk and the use of preterm high mineral containing formulas were routine.<sup>13</sup> One challenge in identifying the prevalence of rickets is the confusion related to terminology. Rickets is defined by radiographic findings, not by any biochemical findings. Standard radiographic definitions of rickets are used. Poorly defined terms, such as osteopenia or biochemical rickets, are often used in the literature interchangeably with radiographically defined rickets. Rickets is not widely reported in preterm infants with birth weight >1500 g unless there are health issues severely limiting enteral nutrition.

Limited long-term studies of bone mineralization exist in former preterm infants. In general, these studies do not demonstrate significant long-term negative effects on bone health in preterm infants who demonstrate catch-up growth occurring during the

first 2 years after birth.<sup>14</sup> A single study demonstrated a small decrease in young adolescent height when the alkaline phosphatase concentration exceeded 1200 IU/L.<sup>15</sup> That study was limited because of the use of formulas containing relatively low amounts of energy and protein. The preterm infants had reduced adult height and low lumbar spine bone mineral density compared with population reference data, and the deficits were greatest in those with birth weight <1200 g and those born small for gestational age.<sup>16</sup>

One study indicated a significant decrease in height during the prepubertal years of former very low birth weight (VLBW) infants exposed to dexamethasone for the treatment of bronchopulmonary dysplasia.<sup>17</sup> In addition, Dalziel et al<sup>18</sup> demonstrated that prenatal steroid use did not affect peak bone mass. It appeared that slower fetal growth, rather than preterm birth, predicted lower peak bone mass. The lower peak bone mass in those born small for gestational age was appropriate for their adult height.

### IN-HOSPITAL ASSESSMENT AND MANAGEMENT

A summary of high-risk factors for the development of rickets is shown in Table 1. It is common medical practice to assess VLBW infants biochemically for evidence of abnormalities of bone-related parameters, especially the serum alkaline phosphatase activity (APA) and serum phosphorus concentration, and subsequently to evaluate them

radiographically if these evaluations suggest a high risk of developing rickets. No absolute values for a low serum phosphorus concentration exist, with values below ~4 mg/dL often, but not always, being considered associated with low phosphorus status. On the other hand, there is little, if any, evidence supporting measuring bone mineral-related laboratory values in infants with birth weight >1500 g unless infants are unable to achieve full feeds or have other conditions, such as severe cholestasis or renal disease, placing them at risk for bone loss.

Typically, a very high serum APA (>1000 IU/L) is suggestive, but not proof, of rickets. In 1 study, values >1000 IU/L were associated with an incidence of radiologic rickets of ~50% to 60%,<sup>12</sup> although some cases were also seen with serum APA in the range of 800 to 1000 IU/L. Elevations of serum APA and clinical rickets are uncommon in the first 4 weeks after birth at any gestational age. Therefore, screening the serum APA and serum phosphorus at 4 to 6 weeks after birth in VLBW infants followed by biweekly monitoring is appropriate. Typically, the APA will peak at 400 to 800 IU/L and then decrease in VLBW infants who do not develop rickets. In this circumstance, clinical experience indicates that if the infant has APA values in this range and has achieved full feeds of human milk with a mineral-containing fortifier or formula designed for preterm infants, there is minimal, if any, risk of developing rickets, and measurement of APA can usually be stopped.

**TABLE 1** High-Risk Criteria for Rickets in Preterm Infants

Born at <27 weeks' gestation
Birth weight <1000 g
Long-term parenteral nutrition (eg, >4 to 5 weeks)
Severe bronchopulmonary dysplasia with use of loop diuretics (eg, furosemide) and fluid restriction
Long-term steroid use
History of necrotizing enterocolitis
Failure to tolerate formulas or human milk fortifiers with high mineral content

Other markers of bone status include serum osteocalcin concentration and bone-specific APA; the latter has been considered of value in cases of cholestasis to help identify the bone-related fraction from total APA. At present, there are no data demonstrating clinical utility of measuring serum osteocalcin concentration and bone-specific APA in neonates, and normal values do not exist for preterm infants. Backstrom et al<sup>19</sup> found no additional information gained from measurement of bone-specific APA compared with total APA in preterm infants. It is, therefore, unlikely that these laboratory values, which are poorly standardized in neonates and expensive to obtain, will be a substantial aspect of clinical decision-making in an individual infant.

The ultimate diagnosis of rickets requires a radiographic evaluation, usually of either the wrist or the knee. Chest radiographs revealing abnormalities of the ribs may be suggestive of rickets, but a confirmatory long-bone film of the wrist or knee should be obtained to confirm the diagnosis. The radiologist should categorize the infant as likely having or not having rickets. Nonspecific terms, such as "osteopenia" or "washed out bones," have little clinical meaning. Rickets in preterm infants appears radiographically similar to rickets in older infants and should be characterized as such. The use of either bone ultrasonography or, before discharge, dual energy radiographic absorptiometry to evaluate bone status may be considered. However, the lack of data related to normal values in former

preterm infants indicate that these are performed primarily for research purposes. Current data do not support routine use of any of these techniques for preterm infants, including those with abnormal radiographic findings.

### CALCIUM AND PHOSPHORUS INTAKE AND ABSORPTION

Rickets in preterm infants is almost always attributable to decreased total absorbed calcium and phosphorus. Decreases in absorption can result from either low intake or low absorption efficiency.<sup>20</sup> Several studies have revealed that, in healthy preterm infants, calcium absorption averages ~50% to 60% of intake,<sup>21–24</sup> which is similar to that of breastfed full-term infants.<sup>1</sup> In contrast, phosphorus absorption is typically 80% to 90% of dietary intake.<sup>25</sup>

Unfortified human milk, parenteral nutrition, and infant formulas designed for full-term infants, including amino acid-based and soy-based formulas, do not contain enough calcium and phosphorus to fully meet the needs for bone mineralization in preterm infants. Even at very high rates of absorption (eg, 80% or more), the calcium and phosphorus intakes from unfortified human milk or formulas not intended for preterm infants would be a limiting factor in bone growth.<sup>20</sup> Table 2 provides sample numbers for the intake, absorption, and retention of calcium in a VLBW infant fed fortified human milk or a formula for preterm infants typically used in the United States compared with unfortified human milk.

Although most attention is focused on calcium intake, the very high urinary calcium concentrations found in preterm infants fed unfortified human milk suggests that phosphorus deficiency is at least as important, if not more important, than calcium deficiency in the etiology of this disease.<sup>4,25,26</sup> Some cases of hypercalcemia have been reported in preterm infants fed unfortified human milk as a result of the very low phosphorus content and resultant relative excess of calcium.<sup>27</sup>

### VITAMIN D IN PRETERM INFANTS

Vitamin D enhances the absorption of calcium, and in general, calcium absorption efficiency is greater in people whose calcium intake is low and in whom vitamin D-dependent absorption increases. However, in preterm infants, the calcium absorption fraction appears to be relatively constant across a wide range of intakes. It has been suggested<sup>21</sup> that most calcium absorption may not be vitamin D dependent in preterm infants in the first month after birth but rather occurs primarily via a passive, paracellular absorption. This hypothesis is unproven, however, and the exact timing and proportion of vitamin D-dependent absorption of calcium and phosphorus in preterm infants is unknown. Some older data suggest an effect of high-dose vitamin D on calcium absorption, but these data have not been verified by using isotopic techniques nor performed on groups of infants using currently available high mineral-containing diets.<sup>5</sup>

**TABLE 2** Approximate Calcium Balance in a Typical Infant Receiving 120 kcal/kg Per Day Intake

	Calcium Concentration (mg/dL)	Intake (mg/kg per day)	Absorption %	Total Absorption (mg/kg per day)	Approximate Retention (mg/kg per day)
Human milk <sup>a</sup>	25	38	60	25	15–20
Preterm formula/fortified human milk	145	220	50–60	120–130	100–120

<sup>a</sup> Human milk assumed to be 20 kcal/oz, and preterm formula and fortified human milk assumed to be 24 kcal/oz.

**TABLE 3** Intakes of Calcium, Phosphorus, and Vitamin D From Various Enteral Nutrition Feedings at 160 mL/kg Per Day Used in the United States

	Unfortified Human Milk <sup>a</sup> (20 kcal/oz)	Fortified Human Milk <sup>a</sup> (24 kcal/oz)	Preterm Formula (24 kcal/oz)	Transitional Formula (22 kcal/oz)
Calcium (mg/kg)	37	184–218	210–234	125–144
Phosphorus (mg/kg)	21	102–125	107–130	74–80
Vitamin D (IU/day) <sup>b</sup>	2.4	283–379	290–468	125–127

<sup>a</sup> Human milk data based on mature human milk.<sup>38</sup>

<sup>b</sup> Based on an infant weighing 1500 g.

It is accepted that the best available marker of vitamin D exposure and vitamin D status is the serum 25-OH-D concentration.<sup>1</sup> Although the active form of vitamin D is 1,25 dihydroxyvitamin D, its serum value is not closely associated with overall outcomes or vitamin D exposure.<sup>1</sup> Therefore, excluding rare cases of severe renal disease or suspicion of vitamin D-resistant rickets, vitamin D status in preterm infants as well as older infants should be monitored exclusively by measuring the serum 25-OH-D concentration, not the 1,25 dihydroxyvitamin D concentration.

Data on the relationship between vitamin D intake and serum 25-OH-D in preterm infants are extremely limited. Backstrom et al<sup>28</sup> found that an intake of 200 IU/kg in the first 6 weeks after birth led to mean 25-OH-D concentrations of ~50 nmol/L and 80 nmol/L by 12 weeks of age (to convert from nmol/L to ng/mL, divide by 2.5). Similar results were found by Koo et al.<sup>29</sup> Most full-term infants achieve 25-OH-D concentrations of more than 50 nmol/L with vitamin D intakes of 400 IU/day.<sup>1</sup> However, it is difficult to extrapolate data from full-term infants to preterm infants, especially those who are hospitalized, in whom UV B-mediated vitamin D formation is likely to be minimal and in whom fat mass, in which vitamin D and its metabolites are stored, is minimal. A recent study revealed a high incidence of very low 25-OH-D concentrations in the cord blood of Arab preterm infants in the Middle East, likely attributable to very low maternal vitamin D status.<sup>30</sup>

## CARE OF VLBW INFANTS RELATED TO BONE HEALTH

### Calcium, Phosphorus, and Vitamin D

The basic approach to prevention of rickets in preterm infants is the use of diets containing high amounts of minerals. In almost all infants with birth weight <1800 to 2000 g, regardless of gestational age, it is recommended to use formulas designed for preterm infants or human milk supplemented with fortifiers designed for use in this population. Bone mineral content is low in infants who are small for gestational age, leading to the recommendation to use these products on the basis of weight rather than gestational age.<sup>31</sup> Further research is needed, however, to clarify whether this is appropriate practice for all preterm infants with birth weight <2000 g.

In the United States, fortified human milk and formulas designed for preterm infants provide calcium intakes of ~180 to 220 mg/kg per day and approximately half that amount of phosphorus (Table 3). Two widely used sets of recommendations in the United States from Tsang et al<sup>32</sup> and Klein et al<sup>33</sup> (Table 4) are consistent with these intakes, and for calcium, it

is reasonable to adopt the lower value and the higher value of the 2 as a range for recommended intakes (ie, 150 to 220 mg/kg per day). For phosphorus, the lower value of 60 mg/kg per day would lead to a 2:1 ratio or higher with the recommended calcium intakes, and thus, a minimum lower intake level of 75 mg/kg per day is recommended to provide a calcium-to-phosphorous ratio less than 2:1. Although no optimal calcium-to-phosphorous ratio is identified, generally a 1.5 to 1.7:1 ratio may be optimal for preterm infants.<sup>34</sup> For an upper intake recommendation for phosphorous, the higher value of 140 mg/kg per day is suggested. As noted later, phosphorus deficiency may occur in some preterm infants, and thus, a higher upper level recommendation is provided.

Pending further research, using the full-term infant vitamin D intake recommendation of 400 IU/day is appropriate for preterm infants born with birth weight >1500 g. Potential risks related to high 25-OH-D concentrations are unknown, and the established upper tolerable intake of 1000 IU/day for healthy full-term infants may be considered an upper intake for preterm infants as well.

**TABLE 4** Recommendations for Enteral Nutrition for VLBW Infants

	Calcium, mg/kg per day	Phosphorus, mg/kg per day	Vitamin D, IU/day
Tsang et al (2005) <sup>32</sup>	100–220	60–140	150–400 <sup>a</sup>
Klein (2002) <sup>33</sup>	150–220	100–130	135–338 <sup>b</sup>
Agostoni <sup>c</sup> (2010) <sup>5</sup>	120–140	65–90	800–1000
This AAP clinical report	150–220	75–140	200–400

<sup>a</sup> Text says “aim to deliver 400 IU/daily.”

<sup>b</sup> 90–125 IU/kg (total amount shown is for 1.5-kg infant).

<sup>c</sup> Reflects European recommendations.

For VLBW infants, few data are available. Their smaller size may lead to a lower need for vitamin D to achieve adequate 25-OH-D concentrations,<sup>28,29</sup> but further data are needed on this relationship. On the basis of limited data, a vitamin D intake of 200 to 400 IU/day for VLBW infants is recommended. This intake should be increased to 400 IU/day when weight exceeds ~1500 g and the infant is tolerating full enteral nutrition. Because this would require supplemental vitamins being added in addition to available human milk fortifiers, some may wish to wait until weight is closer to 2000 g to provide a full 400 IU/day because of concern about the osmolarity of vitamin supplements. These intake recommendations should be subject to clinical trials with rickets and fractures as clinical outcomes.

### Comparisons With Other Recommendations

In Europe, a considerably lower target for calcium and phosphorus intake is common (Table 4). European guidelines generally suggest higher intakes of vitamin D of 800 to 1000 IU/day,<sup>4,5</sup> but there is no direct comparison of this approach compared with the approach used in the United States. Although this vitamin D intake is likely safe and is within the tolerable upper intake limit of the IOM for full-term infants,<sup>1</sup> no data are available for groups of VLBW infants and especially infants with birth weight <1000 g to assess the safety of providing these vitamin D intakes, which, on a body-weight basis may be 5 to 10 times the amount recommended for full-term neonates.

As noted by the IOM report,<sup>1</sup> there are no clinical outcome data to support routine measurement of vitamin D concentrations in preterm infants. Infants with cholestasis, other

malabsorptive disorders, or renal disease should be considered for assessment, targeting a 25-OH-D concentration >50 ng/mL.<sup>1,3</sup> Preterm infants with radiologic evidence of rickets or high APA (>800 IU/L) are often provided the tolerable upper intake total of 1000 IU/day of vitamin D; however, no evidence-based data are available to support any specific benefit to this practice.

Research in a small number of preterm infants has suggested improvement in bone mineral content with an exercise or physical therapy program for preterm infants. No studies have demonstrated a decrease in rickets or fractures with such a program. Care would need to be taken because of the fragile nature of the preterm infants' bones. At present, this therapy requires further clinical investigation before it can be recommended for routine use.<sup>35</sup>

### OTHER MANAGEMENT ISSUES

Despite the use of feedings with high mineral content, some infants may develop rickets. The management of infants who have rickets and remain dependent on intravenous nutrition is beyond the scope of this review, but in general, maximizing calcium and phosphorus intake from intravenous nutrition while minimizing factors that lead to mineral loss (steroids, some

diuretics) is advised. Management approaches for infants who are fed enterally are described in Table 5. These principles have not been tested in controlled trials but reflect expert opinion related to mineral intake and metabolism.

Whether minerals should be added directly to human milk separate from the use of human milk fortifiers is controversial. This practice has been advocated, combined with monitoring of urinary calcium and phosphorus.<sup>36</sup> Although shown to be effective in some small studies, adding minerals directly to human milk, especially in the absence of using human milk fortifiers, is not widely performed in the United States for routine management of VLBW infants, because individually supplementing these minerals does not also provide the extra protein and other nutrients needed for growth.

However, in some infants who have evidence of rickets, the need for fluid restriction or inability to tolerate formula designed for preterm infants or human milk fortifier may lead to the need to directly supplement calcium and phosphorus. Optimal or safest forms and doses of calcium and phosphorus to add directly to the diet of preterm infants are unknown. In general, most widely used is calcium glubionate, a liquid form of calcium

**TABLE 5** Management Approach for Enterally Fed Preterm Infants With Radiologic Evidence of Rickets

1. Maximize nutrient intake. Consider increasing human milk fortifier and/or feeding volume of preterm formula, as clinically indicated. If unable to tolerate human milk fortifier or preterm formula, then will likely need elemental minerals added as described below.
2. If no further increases in these can be made, add elemental calcium and phosphorus as tolerated. Usually beginning at 20 mg/kg per day of elemental calcium and 10–20 mg/kg per day elemental phosphorus and increasing, as tolerated, usually to a maximum of 70–80 mg/kg per day of elemental calcium and 40–50 mg/kg per day elemental phosphorus.
3. Evaluate cholestasis and vitamin D status. May consider measuring 25-OH-D concentration, targeting serum 25-OH-D concentration of >20 ng/mL (50 nmol/L).
4. Follow serum phosphorus concentration and serum APA weekly or biweekly.
5. Recheck radiographs for evidence of rickets at 5- to 6-week intervals until resolved.
6. Advise caregiving team to be cautious in handling of infant.
7. Limit use of steroids and furosemide, as clinically feasible.

containing 23 mg/mL of elemental calcium for oral supplementation. When needed, starting doses of 20 mg/kg per day of elemental calcium may be used, increasing slowly to a maximum of approximately 60 to 70 mg/kg per day of elemental calcium. Data specific to the use of calcium carbonate are not available, but the high pH of the neonatal intestine may make calcium carbonate less than ideal. Calcium gluconate (9.3 mg/mL elemental calcium) may also be used. Salts that contain both calcium and phosphorus are also used.<sup>23</sup> For example, calcium tribasic phosphate contains 0.39 mg calcium and 0.28 mg of phosphorus per milligram of powder, although calcium tribasic phosphate must be compounded as a liquid for administration to infants.

A special population is older preterm infants who develop a low serum phosphorus concentration, often in conjunction with a serum APA <500 IU/L. The specific cause of this low serum phosphorus concentration is unknown, but it is likely partly related to the use of phosphorus in nonbone tissue, such as muscle. The exact serum phosphorus concentration for which evidence demonstrates a need to supplement phosphorus without calcium is not known, but a serum concentration below ~4.0 mg/dL, especially if present for more than 1 to 2 weeks, suggests consideration of adding phosphorus directly.

An ideal oral form of phosphorus for use in preterm infants does not exist. Administering the intravenous preparations orally can be considered, because they are lower in osmolality than are commercially available phosphorus-containing liquids. For example, potassium phosphate provides 31 mg of elemental phosphorus per millimole, and a dose of 10 to 20 mg/kg per day of elemental phosphorus is reasonable and will likely

resolve hypophosphatemia in most preterm infants.

### Transitioning Off High-Mineral Containing Products

Decreasing mineral intake, by either using less human milk fortifier or discontinuing the use of formulas for preterm infants, is often begun at a body weight of ~2000 g. Delaying the switch to transitional formulas and continuing the use of formula designed for preterm infants or human milk fortifier should be considered for infants on fluid restriction, especially <150 mL/kg per day, or for infants with a prolonged course of parenteral nutrition and a persistent elevation of serum APA (ie, >800 IU/L). Use of formula designed for preterm infants would likely be safe until body weight of at least 3000 g is reached, after which some concern might be present about vitamins or minerals (especially vitamin A) exceeding the established tolerable upper intake levels.<sup>37</sup> No clinical evidence of vitamin A toxicity exists, although for intakes slightly above the upper level, a risk-benefit assessment may need to be performed regarding use of formulas designed for preterm infants in some larger infants.

Preterm infants who do not tolerate cow milk protein or lactose-containing products represent a special circumstance. Amino acid-based, soy-based, and other specialized infant formulas generally have higher levels of minerals than do routine infant formulas, but the bioavailability of these minerals, especially in high-risk infants such as those with a history of feeding intolerance or intestinal failure, is uncertain. As such, biochemical monitoring may need to be continued for an extended period of time, and in some cases, direct supplementation with added minerals should be considered.

### POSTDISCHARGE MANAGEMENT OF PRETERM INFANTS

VLBW infants who are discharged exclusively breastfeeding will often do well from a bone mineral perspective; however, they may be at risk for a very high serum APA after discharge. No specific research or clinical studies have addressed this issue. A measurement of serum APA 2 to 4 weeks after discharge is appropriate in exclusively breastfed former VLBW infants, with careful follow-up for values >800 IU/L and consideration of direct mineral supplementation if serum APA exceeds 1000 IU/L. Parents may also choose to provide some feedings per day of a higher mineral-containing formula (such as transitional formulas at 22 kcal/oz) to infants with birth weight <1500 g after hospital discharge. Transitional formulas contain 22 kcal/oz, and their nutrient contents are between those used for full-term infants and those used for preterm infants.

No data are available to define the length of time exclusively breastfed infants receiving such formula supplements or transitional formula need to continue them. This decision is often driven by growth in weight, head circumference, and length, not by bone mineral concerns. Infants consuming less than ~800 mL of currently marketed transitional formula daily after discharge from the hospital will receive <400 IU/day of vitamin D for several weeks to several months. It is reasonable to supplement these infants with a small amount of vitamin D (often 200 to 400 IU/day) to ensure a total intake of at least 400 IU/day.

From a bone mineral perspective, infants with birth weight 1500 to 2000 g will generally do well with exclusive breastfeeding or routine infant formula after discharge from the hospital. Some pediatricians choose to use a transitional infant formula after

infants reach ~34 weeks' postmenstrual age or ~1800 to 2000 g body weight.

There are no specific studies related to the bone mineral needs of infants who are "late preterm" (ie, 34–36 weeks' gestation and >2000 g at birth). However, there are no clinical reports of mineral deficiency or rickets in this population whether breastfed exclusively or fed formula designed for preterm infants, as long as long-term vitamin D status is adequate. Therefore, it is likely that late preterm infants do not generally need special management related to bone minerals after discharge from the hospital. Breastfed preterm infants who are at home should receive 400 IU/day of vitamin D. Formula-fed preterm infants receiving formulas designed for full-term infants would generally not achieve an intake of 400 IU/day of vitamin D until consuming ~800 mL of formula daily, depending on the formula. Providing these infants with an additional 200 to 400 IU/day may be considered, but there are no data indicating any clinical benefit to this practice.

Small-for-gestational-age infants at or near term, such as is common in many global settings, may usually be provided minerals in the same way as larger infants of the same gestational age. Such infants should be monitored carefully for growth, and an adequate intake of vitamin D should be ensured.

## REFERENCES

1. Institute of Medicine. *Dietary Reference Intakes for Vitamin D and Calcium*. Washington, DC: The National Academies Press; 2011
2. Wagner CL, Greer FR; American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*. 2008;122(5):1142–1152

## SUMMARY

1. Preterm infants, especially those <27 weeks' gestation or with birth weight <1000 g with a history of multiple medical problems, are at high-risk of rickets.
2. Routine evaluation of bone mineral status by using biochemical testing is indicated for infants with birth weight <1500 g but not those with birth weight >1500 g. Biochemical testing should usually be started 4 to 5 weeks after birth.
3. Serum APA >800 to 1000 IU/L or clinical evidence of fractures should lead to a radiographic evaluation for rickets and management focusing on maximizing calcium and phosphorus intake and minimizing factors leading to bone mineral loss.
4. A persistent serum phosphorus concentration less than ~4.0 mg/dL should be followed, and consideration should be given for phosphorus supplementation.
5. Routine management of preterm infants, especially those with birth weight <1800 to 2000 g, should include human milk fortified with minerals or formulas designed for preterm infants (see Table 4 for details).
6. At the time of discharge from the hospital, VLBW infants will often be

provided higher intakes of minerals than are provided by human milk or formulas intended for term infants through the use of transitional formulas. If exclusively breastfed, a follow-up serum APA at 2 to 4 weeks after discharge from the hospital may be considered.

7. When infants reach a body weight >1500 g and tolerate full enteral feeds, vitamin D intake should generally be ~400 IU/day, up to a maximum of 1000 IU/day.

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7. Ellis KJ, Shypailo RJ, Schanler RJ. Body composition of the preterm infant. *Ann Hum Biol.* 1994;21(6):533–545
8. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. *J Bone Miner Res.* 2011;26(10):2341–2357
9. Nassar N, Halligan GH, Roberts CL, Morris JM, Ashton AW. Systematic review of first-trimester vitamin D normative levels and outcomes of pregnancy. *Am J Obstet Gynecol.* 2011;205(3):208.e1–208.e7
10. Abrams SA. In utero physiology: role in nutrient delivery and fetal development for calcium, phosphorus, and vitamin D. *Am J Clin Nutr.* 2007;85(2):604S–607S
11. Brannon PM, Picciano MF. Vitamin D in pregnancy and lactation in humans. *Annu Rev Nutr.* 2011;31:89–115
12. Mitchell SM, Rogers SP, Hicks PD, Hawthorne KM, Parker BR, Abrams SA. High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support. *BMC Pediatr.* 2009;9:47
13. Lyon AJ, McIntosh N, Wheeler K, Williams JE. Radiological rickets in extremely low birthweight infants. *Pediatr Radiol.* 1987;17(1):56–58
14. Schanler RJ, Burns PA, Abrams SA, Garza C. Bone mineralization outcomes in human milk-fed preterm infants. *Pediatr Res.* 1992;31(6):583–586
15. Lucas A, Brooke OG, Baker BA, Bishop N, Morley R. High alkaline phosphatase activity and growth in preterm neonates. *Arch Dis Child.* 1989;64(7 Spec No):902–909
16. Fewtrell MS, Williams JE, Singhal A, Murgatroyd PR, Fuller N, Lucas A. Early diet and peak bone mass: 20 year follow-up of a randomized trial of early diet in infants born preterm. *Bone.* 2009;45(1):142–149
17. Wang D, Vandermeulen J, Atkinson SA. Early life factors predict abnormal growth and bone accretion at prepuberty in former premature infants with/without neonatal dexamethasone exposure. *Pediatr Res.* 2007;61(1):111–116
18. Dalziel SR, Fenwick S, Cundy T, et al. Peak bone mass after exposure to antenatal betamethasone and prematurity: follow-up of a randomized controlled trial. *J Bone Miner Res.* 2006;21(8):1175–1186
19. Backström MC, Kouri T, Kuusela AL, et al. Bone isoenzyme of serum alkaline phosphatase and serum inorganic phosphate in metabolic bone disease of prematurity. *Acta Paediatr.* 2000;89(7):867–873
20. Atkinson SA. Calcium, phosphorus and vitamin D needs of low birthweight infants on various feedings. *Acta Paediatr Scand Suppl.* 1989;351:104–108
21. Bronner F, Salle BL, Putet G, Riog J, Senterre J. Net calcium absorption in premature infants: results of 103 metabolic balance studies. *Am J Clin Nutr.* 1992;56(6):1037–1044
22. Hicks PD, Rogers SP, Hawthorne KM, Chen Z, Abrams SA. Calcium absorption in very low birth weight infants with and without bronchopulmonary dysplasia. *J Pediatr.* 2011;158(6):885–890, e1
23. Schanler RJ, Abrams SA, Garza C. Mineral balance studies in very low birth weight infants fed human milk. *J Pediatr.* 1988;113(1 pt 2):230–238
24. Abrams SA, Esteban NV, Vieira NE, Yergye AL. Dual tracer stable isotopic assessment of calcium absorption and endogenous fecal excretion in low birth weight infants. *Pediatr Res.* 1991;29(6):615–618
25. Rowe J, Rowe D, Horak E, et al. Hypophosphatemia and hypercalciuria in small premature infants fed human milk: evidence for inadequate dietary phosphorus. *J Pediatr.* 1984;104(1):112–117
26. Sann L, David L, Loras B, Lahet C, Frederich A, Bethenod M. Neonatal hypercalcemia in preterm infants fed with human milk. *Helv Paediatr Acta.* 1985;40(2–3):117–126
27. Sann L, Loras B, David L, et al. Effect of phosphate supplementation to breast fed very low birthweight infants on urinary calcium excretion, serum immunoreactive parathyroid hormone and plasma 1,25-dihydroxy-vitamin D concentration. *Acta Paediatr Scand.* 1985;74(5):664–668
28. Backström MC, Mäki R, Kuusela AL, et al. Randomised controlled trial of vitamin D supplementation on bone density and biochemical indices in preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 1999;80(3):F161–F166
29. Koo WW, Krug-Wispe S, Neylan M, Succop P, Oestreich AE, Tsang RC. Effect of three levels of vitamin D intake in preterm infants receiving high mineral-containing milk. *J Pediatr Gastroenterol Nutr.* 1995;21(2):182–189
30. Dawodu A, Nath R. High prevalence of moderately severe vitamin D deficiency in preterm infants. *Pediatr Int.* 2011;53(2):207–210
31. Lapillonne A, Braillon P, Claris O, Chatelain PG, Delmas PD, Salle BL. Body composition in appropriate and in small for gestational age infants. *Acta Paediatr.* 1997;86(2):196–200
32. Tsang RC, Uauy R, Koletzko B, Zlotkin SH, eds. *Nutrition of the Preterm Infant: Scientific Basis and Practical Guidelines*, 2nd ed. Cincinnati, OH: Digital Educational Publishing Inc; 2005
33. Klein CJ. Nutrient requirements for preterm infant formulas. *J Nutr.* 2002;132(6 suppl 1):1395S–1577S
34. Rowe JC, Goetz CA, Carey DE, Horak E. Achievement of in utero retention of calcium and phosphorus accompanied by high calcium excretion in very low birth weight infants fed a fortified formula. *J Pediatr.* 1987;110(4):581–585
35. Schulzke SM, Trachsel D, Patole SK. Physical activity programs for promoting bone mineralization and growth in preterm infants. *Cochrane Database Syst Rev.* 2007;(2):CD005387
36. Trotter A, Pohlandt F. Calcium and phosphorus retention in extremely preterm infants supplemented individually. *Acta Paediatr.* 2002;91(6):680–683
37. Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academies Press; 2001
38. American Academy of Pediatrics, Committee on Nutrition. *Pediatric Nutrition Handbook*. Kleinman RE, ed. 6th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009

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