

In utero physiology: role in nutrient delivery and fetal development for calcium, phosphorus, and vitamin D¹⁻⁴

Steven A Abrams

ABSTRACT

Only limited aspects of the transfer of calcium across the placenta to the fetus are known. Clinical outcome studies suggest that bone mineral mass in newborn infants is related to maternal size and dairy intake. Available data indicate that vitamin D deficiency may also limit in utero fetal bone mineral accumulation. Recent data suggest that maternal vitamin D status affects long-term childhood bone status. At present, no strong evidence exists showing that improving maternal calcium or vitamin D status has a long-term positive effect on childhood bone mass. In premature infants, clinical rickets and fractures are common. In utero rates of calcium accretion during the third trimester cannot be readily achieved. The use of fortifiers designed for human-milk-fed infants or specially designed high-mineral-containing formulas allows for bone mineral accretion at or near in utero rates. Recent data have shown that physical therapy programs, judiciously used, in combination with adequate mineral content, can enhance bone mineral mass in preterm infants. There is little evidence for the use of high doses of vitamin D in the management of premature infants. After hospital discharge, continuation of a relatively high mineral intake has been shown to enhance bone mineral acquisition. Future research should include evaluations of the role of maternal vitamin D supplementation on fetal and infant bone mass, the mineral needs of infants weighing <800 g or <25 wk gestation, and the optimal discharge management of premature infants who are at risk of low bone mass. *Am J Clin Nutr* 2007; 85(suppl):604S–7S.

KEY WORDS Human milk, calcium absorption, premature infants, infant nutrition, fetal growth

TRANSPLENTAL MINERAL TRANSFER AND BONE GROWTH

The factors affecting transplacental calcium transport are poorly defined. A total of 30 g Ca is accumulated in the fetus, most of this during the third trimester. The calcium concentration in a third-trimester fetus is greater than in the maternal plasma, which indicates the need for active transport across the placenta (1).

Recent animal data regarding the factors affecting fetal calcium transport were reviewed by Belkacemi et al (2). A role for multiple calcium-binding proteins in this process has been identified. Much less clear are the roles of vitamin D, estrogen, and parathyroid hormone. Maternal 1,25-dihydroxyvitamin D concentrations increase during the third trimester, and vitamin D is synthesized in the placenta. Furthermore, it is possible that vitamin D increases the synthesis of various calcium-binding proteins.

Human studies have provided mixed data. In general, maternal calcium supplementation has not been shown to affect newborn bone mineral mass in populations with adequate baseline intakes (3). Fetal calcium needs are primarily met by increased calcium absorption during pregnancy. For these reasons, no recommendation exists in the United States to increase calcium intake during pregnancy above the Adequate Intake of 1000 mg/d for adults and 1300 mg/d for adolescents (4).

However, the results of several studies have suggested that very low maternal calcium intakes may be a risk for lower bone mass in neonates. These data include a study in India in which bone mineral density in infants was significantly related to maternal bone mass (5). In a controlled trial of calcium supplementation during pregnancy in the United States, mothers with a low habitual calcium intake (<600 mg/d) who were provided calcium supplementation delivered infants with a greater bone mineral mass than in infants whose mothers were not supplemented (6). In a group of pregnant African American adolescents with a mean age of 16 y, nutrition was significantly related to fetal femur growth during pregnancy, such that dairy intakes of <2 servings/d were associated with lower fetal bone development than were greater intakes of dairy (7).

In general, limited available data are consistent with a target intake for calcium during pregnancy at least near the age-appropriate Adequate Intake. However, special circumstances, including multiple gestation or adolescent pregnancy may pose a particular risk for both fetal and maternal bone mineral status.

Data relating to vitamin D and fetal bone growth are limited. A recent study of 198 children born in the United Kingdom indicated that the maternal use of vitamin D supplements was

¹ From the US Department of Agriculture/Agricultural Research Service, Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX.

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⁴ Reprints not available. Address correspondence to SA Abrams, USDA/ARS Children's Nutrition Research Center, 1100 Bates Street, Houston, TX 77030. E-mail: sabrams@bcm.edu.

significantly associated with greater childhood bone mineral mass (8). In particular, very low maternal concentrations of serum 25-hydroxyvitamin D were associated with lower bone mineral mass in the offspring at 9 y of age. The implications of this finding for prenatal nutritional care are uncertain. Of note is that there are no convincing data to support a relation between infant feeding (breast milk versus formula) and long-term bone mineral mass, although total calcium absorption is generally lower in breast-fed than in formula-fed infants. It is possible that in utero events are more important in this regard than are infant feeding practices, but this is not clear from studies in animal models or premature infants (9).

An additional line of evidence suggestive of a relation between maternal vitamin D status and infant bone metabolism is derived from studies of the effect of season of delivery on infant bone mineral mass. Namgung and Tsang (1) describe results from white infants delivered in Cincinnati, OH, showing greater neonatal bone mineral mass in the winter but not the summer. In contrast, in Korea, bone mineral mass was greater in infants born during the summer than during the winter. The authors speculate that the different effects in these 2 locations may be due to a high frequency of very low maternal vitamin D status during the winter in Korea, which may lead to frank vitamin D deficiency in the mother and infant. In the United States, where severe vitamin D deficiency is uncommon, high vitamin D status during early pregnancy (summertime for winter-born infants) may improve bone mineral mass at delivery. Regardless, these data do not allow for clear recommendations about timing and amount of vitamin D supplementation during pregnancy to optimize bone mass in infancy or later in life.

MINERAL NEEDS OF PREMATURE INFANTS

Premature infants, especially those weighing <1500 g at birth (very low birth weight, or VLBW), are at risk of significant mineral deficiencies. Although some nutrients are initially increased in the milk of mothers who deliver prematurely, the amounts of calcium, phosphorus, protein, and other bone mineral nutrients in unfortified human milk are inadequate to meet the needs of VLBW infants during growth.

Severe mineral deficiencies are commonly identified in VLBW infants regardless of gestational age. This condition, known as “osteopenia of prematurity” or “metabolic bone disease of prematurity,” results in significantly decreased whole-body and regional bone mineral content and density relative to the expected level of the mineral for a fetus of comparable weight or gestational age. Clinical evidence of mineral deficiency may occur in as many as 30–50% of VLBW infants who are fed either unfortified human milk or formulas that are designed for full-term rather than preterm infants (10, 11). Most cases of osteopenia in VLBW infants are related to a deficiency in the 2 primary bone minerals, calcium and phosphorus, rather than vitamin D. The role of other mineral deficiencies, including magnesium and zinc, in this condition is poorly described.

Human milk contains \approx 260 mg Ca/L and 140 mg P/L. Even when VLBW infants are fed at feeding volumes of 180–200 mL/d, assuming calcium absorption of 70% and phosphorus absorption of 80%, this would still only provide about one-third of the in utero level of absorbed calcium and phosphorus (12–14). Although no data exist to conclude exactly which infants should receive fortified human milk, the general consensus is that all

infants with a birth weight <1500 g would benefit from the additional fortification (15). In countries such as the United States where fortifiers are readily available, they are frequently recommended for all human-milk-fed infants weighing <1800–2000 g at birth. The safety of human milk fortification with available products has been shown (15), although further monitoring or research into the safety and benefits of fortifiers is warranted, especially as new products or fortification strategies are developed.

Evaluation of premature infants at risk of osteopenia of prematurity generally includes serum screening with measurement of total or ionized calcium, phosphorus, and alkaline phosphatase activity (16). Bone-specific alkaline phosphatase activity is usually not assessed in the clinical setting, nor are other biochemical markers of bone turnover usually obtained. Both the range of normal values and the effect of growth and disease processes on bone turnover markers are poorly understood in preterm infants, which limits their clinical use.

When these screening values are clearly abnormal, it is often reasonable to obtain a plain film radiograph to assess the bones for possible osteopenia, rickets, or fractures. Screening values to proceed with such radiographic studies should include consideration of the clinical history and physical examination, but we usually recommend radiographic evaluation when serum alkaline phosphatase activity is >800 IU/L, especially when combined with a serum phosphorus concentration <4.5 mg/dL. Although routine radiographs are an insensitive technique for identifying mild osteopenia, they are relatively safe, clinically available, and may be useful in identifying severe bone loss and rickets that would require adjustment of clinical care strategies.

Radiographs of the wrist or knee are usually obtained, and chest radiographs obtained for other clinical indications may be evaluated as well. Measurements of urine calcium and phosphorus have been useful in some studies but can be difficult to perform and interpret in very small infants and are not widely utilized, especially in the United States. Measurements of serum parathyroid hormone concentrations or vitamin D metabolite concentrations is rarely clinically useful except in infants with long-standing cholestasis.

Bone mineral mass assessment of preterm infants with the use of dual-energy X-ray absorptiometry or similar methods has been done in research studies but not for clinical purposes. More recently, bone ultrasound has been used to evaluate preterm infants. Bone ultrasound in infants uses sound waves to assess the speed of sound (SOS) in a given bone (usually the tibia or heel), which is the transit speed between the transducers of the device. Osteoporotic bone has a lower value for the SOS than does normal bone. This method is easily performed in ventilated infants in an intensive care setting, which is not possible with dual-energy X-ray absorptiometry. Surprisingly, the data suggest that there may not be a large increase in bone SOS in the postnatal period in preterm infants (17, 18). It remains unclear whether this represents a true postnatal decrease in functional strength. Further data relating bone ultrasound results to functional outcomes both during and after the hospitalization of preterm infants are needed.

One area of interest is the use of physical activity—especially passive range-of-motion exercise—in preterm infants. Recent evidence shows that these exercises lead to an increase in bone mineral mass (19) and may attenuate the postnatal decline in ultrasound-determined bone mineral status in preterm infants



(20). Much more research is needed, however, to clarify the type, duration, and safety of exercise or physical therapy interventions as well as the optimal target group in a neonatal setting. For now, it is important to ensure that such programs are done by highly trained personnel in infants with adequate mineral intake so as to not promote unnecessary fractures.


Although osteopenia of prematurity is primarily a disease of inadequate mineral intake, not vitamin D deficiency, it is unclear how much vitamin D-dependent calcium absorption occurs in preterm infants, especially in the first weeks of life (21, 22). Available data suggest adequate 25-hydroxyvitamin D concentrations in infants with relatively low dietary intake and no evidence of short- or long-term benefit from high intakes (23). Some concern about toxicity from high vitamin D intakes has been suggested, but no clinical findings are consistent with this concern (24). Vitamin D intakes of 200–400 IU daily are usually recommended for noncholestatic preterm infants. Infants with significant cholestasis require complete evaluation and consideration of other forms of therapy, including the use of calcitriol.

One of the most contentious areas in neonatal nutrition is the need for high calcium and phosphorus intakes in preterm infants, especially those weighing <1500 g at birth, after hospital discharge. Few data exist to clarify the need either for higher protein and mineral-containing infant formula or other methods of mineral supplementation that would be suitable for exclusively breastfed infants (25). The available data suggest increased bone mineral mass in infants who receive formulas containing more minerals than do routine infant formulas and benefits up to ≥ 9 mo of age (26, 27). It is our practice to recommend the use of formula with a higher mineral content after hospital discharge for formula-fed infants with birth weights <1500 g or for those who are restricted in fluid intake because of bronchopulmonary dysplasia.

For breastfed infants with birth weights <1500 g or who are fluid-restricted, consideration can be given to careful monitoring of growth and nutritional status without supplementation. However, if supplementation is chosen, either formula can be added directly to mother's milk for feeding with a bottle or 2–3 formula feeds can be given daily while the mother pumps and saves her milk at those feeding times for later use. For those mothers who do not wish to use any formula products, oral supplementation with calcium and phosphorus can be provided without use of cow milk protein. This approach does not provide protein or other bone mineral micronutrients such as magnesium or zinc. Values of alkaline phosphatase greater than ≈ 1000 –1200 IU/L should be avoided when possible because of to the risk of short- and long-term growth failure and fractures associated with such values (28).

FUTURE RESEARCH NEEDS

Three areas can be defined as being particularly in need of further clinical investigation related to fetal bone mineral metabolism. The first area is the effects on fetal and neonatal bone growth of vitamin D supplementation for mothers at risk of preterm or small-for-gestational-age delivery. Controlled trials in both populations with low and those with high vitamin D status are needed to evaluate the benefits and risks of this intervention. A second area would be further research related to the nutrition needs of extremely preterm infants, such as those weighing <800 g or <25 wk gestation and those who require significant fluid

restriction, related for example, to bronchopulmonary dysplasia. Few data exist relative to the needs of this population related to bone health. Finally, considerable research remains to clarify the optimal length, quantity, and method of providing supplemental minerals and vitamin D after hospital discharge for preterm infants, especially those who are breastfed. 

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