

Zinc for preterm infants: who needs it and how much is needed?^{1–3}

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The establishment of micronutrient requirements for infants remains a challenge. For healthy full-term infants, breast milk is an appropriate standard for virtually all nutrients. In contrast, guidelines for infants who are not healthy, and infants who are born preterm, are much more tenuous.

Although micronutrient research in preterm infants has a long history, most of it has focused on biochemical or nutrient balance outcomes. Much less is known about clinical disease outcomes related to most micronutrients. Approximately 12% of infants in the United States are born preterm, and ~1.5% are born with very low birth weight. For this substantial group of high-risk infants, a lack of micronutrient intake recommendations, and more importantly, lack of outcome data on which to base any recommendations, is a major gap. Dietary guidelines for micronutrients in preterm infants have often been established by working groups or individual authors (1). There are no nutrient intake recommendations specific to preterm infants in the United States equivalent to the Dietary Reference Intakes or the *Dietary Guidelines for Americans*.

One critical micronutrient needed by preterm infants is zinc. Zinc has an important and well-established role in immune function and growth (2). Evidence suggests that the amount of zinc in human milk, like that of other minerals such as calcium and phosphorus, may not be optimal for very preterm infants and that human-milk feedings should be fortified with additional zinc for this population (3). The practice of adding such fortification and the use of preterm formulas with zinc concentrations greater than that of routine formulas is a well-established standard of care for small preterm infants in the United States and many other countries.

Zinc supplements are increasingly being suggested for a variety of pediatric populations, especially in developing countries, to prevent or treat various disease conditions, most notably infections (2). When provided for this purpose, the intake provided is often well above the nutrient requirements. That is, rather than providing the amount of zinc needed to meet tissue accumulation needs on the basis of absorption and excretion of dietary intake, doses are given considerably above that amount to provide a potential pharmacologic effect on disease prevention or treatment.

This approach underlies the dosing provided in a study published in this issue of the *Journal* (3). The authors provided ~10 mg supplemental Zn/d to a group of very-low-birth-weight (<1.5 kg) infants beginning at 1 wk of age and continued supplementation for their hospitalization or until 42 wk post-

menstrual age. Mean weight during the entire intervention period was not provided, but assuming a weight of 1.2–1.5 kg, this dose provided ~6–8 mg Zn/kg during most of the study. A beneficial outcome was shown for morbidity and mortality in the supplemented group compared with the unsupplemented group, primarily driven by a rate of necrotizing enterocolitis (NEC) of zero in the supplemented group. Of note is that growth was comparable between the groups even though the intake in the control group was low. The number of infants in the control group who developed NEC requiring surgery is a crucial outcome that was not provided and might be a better marker than the overall incidence of NEC for evaluating serious disease outcome.

The control group in this study received ~1.3 mg Zn daily ($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$). Although this intake of zinc was previously considered adequate (1), recommendations based on more recent nutrient balance studies indicate a need for a zinc intake of 1.8–2.4 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in very preterm infants to meet tissue accumulation requirements (4, 5). Of note is that routine supplementation strategies using commercially available human-milk fortifiers and preterm formulas in the United States provide ~2 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ of zinc intake. Thus, this study compared an intake unlikely to meet currently described physiologic needs in the population with a pharmacologic dose well above the likely tissue accumulation requirement.

The distinction between a physiologic dose needed for growth and a much higher dose as provided in this type of study is critical. When using supplement doses that are several times the physiologic requirements for growth, concern about toxicity and other complications need to be evaluated in adequately powered controlled trials. In this case, using 10 mg Zn in a situation where copper intake is only ~250 $\mu\text{g}/\text{d}$ and iron intake is often

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<4 mg/d leads to concerns about inhibition of absorption of these key nutrients by the high zinc dose (4–6). In adults, a dose of 15 mg Zn and 3 mg Fe given in water decreased iron absorption by 56% (7) and a zinc:iron molar ratio of 5:1 and above also markedly inhibited iron absorption (8). Similar data are not available for preterm infants, but it seems likely that this would be a concern in any population. The supplement dose used in this study is well above the Tolerable Upper Intake Level for zinc intake set by the Institute of Medicine of 4 mg/d for infants in the first 6 mo of life related to concerns about zinc:copper interactions causing inadequate copper absorption (9).

Therefore, because the United States and many other countries have already adopted a fortification strategy for human milk that provides zinc intakes that approximate more recent nutrient balance-based recommendations, implementation of a pharmacologic supplement strategy cannot be recommended in the United States or other countries without considerable further research. This should include multicentered studies in which critical endpoints that include zinc, copper, and iron status are fully evaluated and in which multiple amounts of zinc supplementation are compared with a control group that meets the current nutritional zinc intake recommendations. Whether there is evidence that the risk:benefit ratio supports the use of pharmacologic amounts of zinc supplementation (eg, $>3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) to justify such a research study would need very careful evaluation before being undertaken.

Meanwhile, these data remind us that inadequate micronutrient intakes are not beneficial to preterm infants and products used to fortify human milk or as infant formulas need to be based on the most recent recommendations, even if the evidence base for them is incomplete. Clear delineation of nutritional compared with pharmacologic benefits is critical to evaluating supplementation

strategies for micronutrients in any population, including in preterm infants.

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