

## Review

# Zinc Deficiency in Nursing Infants

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**Key words:** Zinc-deficiency, iron, breast-milk, fetus, supplementation

Zinc deficiency during nursing can occur even in breast-fed infants. Zinc reserves accumulated during fetal development modulate the infant's susceptibility to zinc deficiency. Improvement of maternal zinc nutrition during pregnancy is the key for infant's zinc nutritional support and prevention of low-for-lactation-age zinc concentrations of breast-milk.

### Key teaching points:

- Maternal zinc-nutritional status can affect zinc-nutrition of breast-fed infants.
- Low-for-lactational-age milk-zinc concentration is associated with zinc deficiency in breast-fed infants.
- Zinc deficiency during breast-feeding may occur because of an infant's low-zinc reserves.
- An intestinal-zinc conservation mechanism modulates perinatal zinc losses.

The nutritional status during early human development is a function of nutrients transferred from the mother through milk and/or deposited as reserves in the fetus during pregnancy. The rapid growth experienced by term infants during the first months of life, while they are still breast-feeding, underscores the teleological suitability of breast-milk. As such, breast-milk is the gold standard frequently used to establish nutrient requirements and recommendations. Therefore, nutrition deficiency in breast-fed infants from apparently healthy mothers has always been considered rare. However, it has been recognized that, in spite of the superiority of breast-milk over other feeding alternatives, at least for some micronutrients, there are special circumstances where full development of breast-fed infants may be compromised.

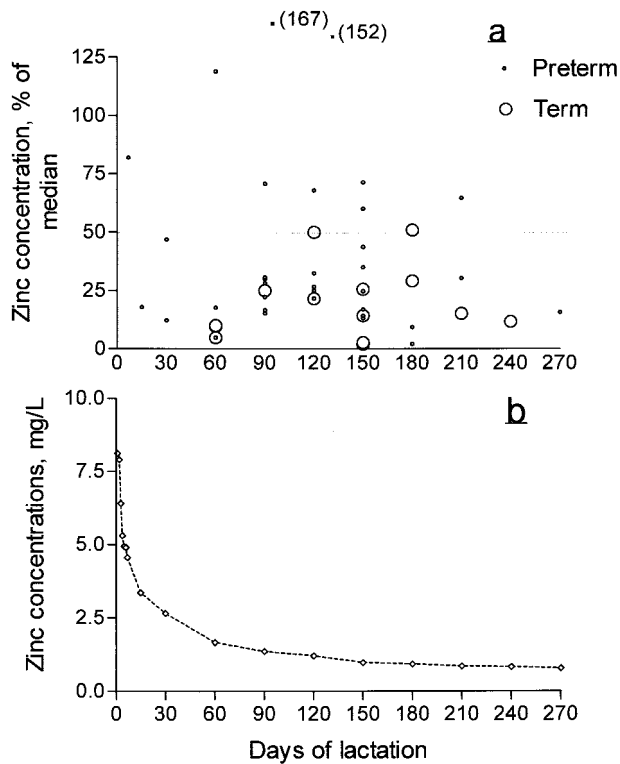
For some trace elements, such as iron and copper, which occur in very low concentrations in breast-milk, the infant is born with liver reserves which are used up during breast-feeding. The infant is also born with zinc reserves; however, this metal in breast-milk occurs at much higher relative concentrations, especially in the first three months. Therefore, risk of deficiency of these elements would be expected only under conditions that would adversely interfere with infants' hepatic storage during fetal development, such as prematurity. As a consequence, low-birth-weight or intra-uterine-growth retardation could limit zinc reserves. In a recent review by Scholl and

Reilly [1], conditions of compromised fetal development were, in the majority of studies, responsive to maternal zinc supplementation. Scholl and Reilly concluded that the studies "provided support for the possible relationship between maternal zinc status and compromised fetal development and fetal growth potential" [1]. Nevertheless, because iron nutrition status of infants decreases with increasing age, its deficiency is considered the most common throughout the world [2]. In spite of low iron and copper in breast-milk, there are no reported deficiencies of these elements associated with exclusive breast-feeding in term infants, a circumstance which is not the case of zinc. Because of the physiological decrease in milk zinc concentrations, especially in the first three months, it was speculated that this element may become a first-limiting nutrient in breast-milk [3].

Clinical zinc deficiency during breast-feeding has frequently been reported and was summarized by Dorea [4]. Cases of zinc deficiency during breast-feeding are accompanied by skin rashes or dermatitis which are the main symptoms, often in combination with failure to thrive, low serum zinc and irritability. Surprisingly, 25% of the cases shown in Fig. 1a were reported in term infants. The age at which symptoms first appeared were earlier in preterms than in term infants. In all cases, zinc therapy corrected the symptoms. A plotting of data

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**Fig. 1.** Graphic representation of data summarized by Dorea [4] showing (a) milk zinc concentrations as percentage of (b) median values of breast-milk zinc concentrations according to days of lactation.

summarized from Dorea [4] illustrates median zinc concentrations throughout lactation (Fig. 1b) and compares the percent of zinc concentrations in breast-milk of mothers whose infants were treated for zinc deficiency (Fig. 1a). All the data in Fig. 1a were from apparently healthy mothers from industrialized countries [4].

The variability reported for mean breast-milk-zinc concentrations is high [4]. Nevertheless when compared to median values the majority of cases of zinc deficient infants showed that they were breast-fed on milk with mean zinc concentrations below median values for the respective age of lactation. Only eight out of 46 case-reports had breast-milk-zinc concentration above 50% of the median. The majority of cases reported zinc concentrations between 2% and 50% of the median zinc concentration for the corresponding lactation age. Indeed the role of breast-milk zinc in maintaining infant zinc status is further illustrated by the study of Atkinson *et al.* [5] describing an occurrence of several cases which I denominated as “low-for-lactation-age milk-zinc concentrations” [4] among apparently healthy mothers. Why milk-zinc may occur in such low concentrations is not fully understood, but animal model studies indicate the existence of specific zinc transporters in the mammary gland. Animal studies showed that lethal milk (lm) mutation in mice caused zinc deficiency in pups nursed by lm dams. A ZnT-4 transporter abundant in mammary gland may be

associated with zinc secretion into milk. A mutation of the ZnT-4 gene accounts for the lethal milk [6].

Comparative studies, testing the hypothesis that compromised maternal-zinc status could influence milk-zinc concentrations, did not show statistically significant differences between controls and undernourished mothers. Also differences in zinc intake arising from geographic, socioeconomic or natural food variation produced no evidence that they could affect milk zinc concentrations [4]. So far, also, studies of maternal zinc supplementation showed no consistent effect on breast-milk-zinc concentration [4]. Even in specific cases of observed infant zinc deficiency, most attempts to raise breast-milk zinc through maternal zinc supplementation failed, regardless of increases in maternal plasma zinc (details in [4]).

In Dorea’s review [4], most supplemental studies were carried out on women in affluent countries. Oral zinc trials on women of low socioeconomic background in less industrialized countries also did not show an increase in breast-milk zinc, although there were claims in differences in the rate of decline of milk zinc between supplemented and non-supplemented mothers, as well as other benefits [4]. The secretion of zinc in human milk is rather complex and apparently associated with specific milk proteins, which *per se* may have a distinct pattern of decline with lactation age. As a result, breast-milk-zinc concentration is a difficult end-point to study. The great variability within and between studies, and also the physiological decline (Figure 1b) observed specially in the first six months, poses a challenge in trial design. Studies of breast-milk enrichment [7] with maternal supplementation of zinc and vitamin B-6 demonstrated that the vitamin, but not zinc, increased in both maternal serum and breast-milk.

Although low zinc concentrations in breast-milk may well be an important contributing factor in infant zinc deficiency during breast-feeding, there are indications of maternal factors during pregnancy modulating the post-natal infant-zinc metabolism. Hepatic fetal zinc [8], possibly as hepatic metallothionein [9], may serve as a source of zinc in the early months of postnatal life together with the provision of zinc in breast-milk and efficiency of a zinc preservation mechanism to maintain the zinc balance of infants.

Events related to infant zinc metabolism modulated during fetal development were apparent in the report by Walravens *et al.* [10]. Failure to thrive in breast-fed infants coincided with concurrent maternal pregnancy. A study by Glover and Atherton [11] reported a woman presenting “low” zinc concentration in two consecutive pregnancies had a breast-fed infant with zinc deficiency. Zinc supplementation during pregnancy seemed to delay zinc deficiency of the second breast-fed infant until eight months of age. In two case studies of women whose breast-feeding infants developed zinc deficiency, maternal zinc therapy prevented zinc deficiency in the nursing infant conceived in the second pregnancy [12–13]. In the study by Murphy *et al.* [14] a preterm infant developed zinc deficiency while

nursing on low breast-milk zinc. However, there was a remarkable increase in milk-zinc in a second lactation without maternal zinc therapy, and the second child from this lactation did not develop zinc deficiency.

A large amount of zinc in the intestinal milieu is found in neonates as a result of the amniotic fluid swollen in the uterus and colostrum intake right after birth, both zinc rich substances. The concentration of zinc intestinal contents exceeds the amount of zinc in colostrum [15] indicating an important loss of endogenous zinc. However, only recently has it been recognized [16] that an intestinal-zinc conservation mechanism is necessary to achieve a positive zinc balance. The abundance of zinc in the newborn intestine coincides with an obligatory negative zinc balance, whose origin and duration has not yet been fully explained. Higashi *et al.* [17] speculated that metabolic events linked to post-conceptual age-modulated endogenous zinc losses in preterm infants were possibly related to the immaturity of the gastrointestinal tract [18]. A gastrointestinal tract which is not fully developed may present metabolic features resembling fasting or malnutrition [19]. Under this hypothesis, luminal concentration of electrolytes, zinc in particular, which are constantly being secreted by the intestinal mucosa may be easily lost and, in turn, compromise zinc absorption [20]. Recently, Krebs *et al.* [21] observed the contribution of unabsorbed fat to interfering with the conservation of endogenous zinc by the gastrointestinal tract in cystic fibrosis patients, confirming earlier observations of the effects of fats on zinc absorption in preterm infants [22]. The degree of organ immaturity shown in preterms, further jeopardized by smaller zinc reserves, may actually explain zinc imbalances. Therefore, a zinc conservation mechanism *per se* or a pathophysiological consequence of a less than ideal nutrient supply is important in the extension and degree of perinatal zinc losses. Because zinc occurs in relatively high concentrations in breast-milk, limitations of zinc nutrition in the breast-fed infant was not recognized until recently [3].

Nutrition deficiency in breast-feeding continues to be rare, but may occur with regard to a specific micronutrient under special circumstances. Recently, Kreiter *et al.* [23] reported 30 cases of rickets in breast-fed infants. In all cases, apparently low concentrations of vitamin D in breast-milk due in part to insufficient exposure to sun light in both mothers and infants was a contributing factor associated with skin pigmentation. All infants were African Americans. Another feature was the age of diagnosis. Except for three cases (5–6 months), the majority occurred between 8 and 25 months (median of 15.5 months).

The duration of exclusive breast-feeding is still debatable, and the basis of discussion is centered on the breast-milk provision of macronutrient (protein) and energy [24]. It is important to recognize the importance of micronutrients as they affect the health of normal and low-birth-weight infants. The specific case of zinc deserves special attention in relation to public health policies and particularly to the Code of Marketing

of Breast Milk Substitutes. Public health policies should also be concerned with improvement of maternal zinc nutrition to provide full reserves of fetal zinc and to sustain a breast-milk-zinc profile compatible with exclusive breast-feeding.

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*Received July 23, 2001; revision accepted December 11, 2001.*