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Minireview

Zinc in neonatal health: a mini-review

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Abstract

Zinc is an essential trace element with catalytic, structural, and regulatory functions relevant to neonatal growth, immune competence, epithelial integrity, neurodevelopment, and metabolic programming. Neonates at greatest risk of zinc deficiency include preterm and very-low-birth-weight infants, growth-restricted newborns, exclusively breastfed infants and infants with prolonged parenteral nutrition, high gastrointestinal losses, or severe systemic disease. This mini-review summarizes current evidence on zinc in neonatal health, with emphasis on biological plausibility, clinical manifestations of deficiency, and the potential benefits and limits of supplementation. Zinc supplementation may improve short-term growth in selected preterm or low-birth-weight infants, while effects on bronchopulmonary dysplasia, long-term neurodevelopment, and other prematurity-related outcomes remain uncertain. Zinc has also been evaluated as an adjunct to phototherapy for neonatal hyperbilirubinemia and as an adjunct to antibiotics in young-infant sepsis, but heterogeneity in populations, dosing, timing, and outcomes precludes routine use. Associations between zinc status and autism spectrum disorder or later cardiometabolic outcomes remain biologically plausible but not clinically proven. Overall, zinc supplementation in neonates should be targeted to documented or strongly suspected deficiency and high-risk clinical contexts, with monitoring for efficacy, safety, and interactions with other trace elements.

Keywords

Zinc, neonate, preterm infant, breast milk, parenteral nutrition, neurodevelopment.

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Introduction

Zinc is an essential trace element present in very small amounts in living organisms, but it has central catalytic, structural, and regulatory roles in several biological processes, including growth, intermediary metabolism, immune defense, gene expression, and tissue repair [1, 2]. Zinc is a component or regulator of numerous enzymes and transcription factors, including nitric oxide synthase, carbonic anhydrase, and zinc-finger proteins; these pathways are relevant to inflammation, cellular respiration, muscle function, vascular homeostasis, DNA synthesis, gene transcription, and intercellular signaling [3-5]. The clinical consequences of zinc deficiency are most evident in the intestine, immune system, somatic growth, skin, and developing nervous system. Deficiency during fetal life, the neonatal period, and early infancy may therefore be particularly relevant in preterm, low-birth-weight, growth-restricted, or clinically unstable infants [6, 7]. The concept of hidden hunger is also relevant to neonatal care: micronutrient deficiency may remain clinically unrecognized despite apparently adequate caloric intake and may coexist with poverty, food insecurity, overweight, or obesity [8, 9]. In this mini-review, we summarize the main roles of zinc in neonatal health, the clinical consequences of deficiency, and the current evidence for zinc supplementation in selected neonatal and pediatric conditions [1-71].

Assessment of neonatal zinc status and supplementation safety

Serum or plasma zinc is commonly used to assess zinc status in neonates, but interpretation is difficult because values vary with gestational age, postnatal age, inflammation, albumin concentration, sampling conditions, recent supplementation, and analytical method [10, 11]. A neonatal zinc concentration below approximately 10.7 μmol/L (70 μg/dL) has been used as a threshold for deficiency in some studies, but cut-offs vary by age, population, and laboratory method; zinc status should therefore be interpreted together with clinical context, nutritional history, growth pattern, inflammatory status, and ongoing losses rather than as an isolated diagnostic marker [10, 12]. Supplementation should be individualized because both deficiency and excess may be clinically relevant. Reported adverse events are generally uncommon, although vomiting or gastrointestinal intolerance may occur, particularly with higher enteral doses; prolonged excessive zinc intake may also interfere with copper metabolism [2, 13]. In neonatal practice, the decision to supplement should integrate biochemical data, intake from enteral and parenteral sources, intestinal losses, growth response, and the risk of interactions with other trace elements.

Zinc and fetal growth restriction

Zinc deficiency during pregnancy has been associated with impaired fetal growth, although causality is complex and likely mediated by multiple nutritional, placental, inflammatory, and oxidative pathways rather than by a single mechanism [7]. Maternal zinc deficiency has also been associated with adverse pregnancy outcomes, including hypertensive disorders, congenital anomalies, and altered development; supplementation may support growth in selected preterm or low-birth-weight infants, but this evidence should not be extrapolated to routine supplementation of all pregnancies or newborns [14, 15]. Clinical studies have reported lower zinc concentrations in umbilical cord blood of neonates with altered intrauterine growth patterns, supporting the hypothesis that fetal zinc status may reflect placental nutrient transfer and intrauterine nutritional exposure [16]. Zinc deficiency may influence pancreatic beta-cell activity, insulin secretion, oxidative stress, mitochondrial function, and placental biology, potentially contributing to disglycemia at birth and later metabolic programming [17, 18]. In growth-restricted newborns (IUGR), zinc status can be considered within a broader nutritional and metabolic assessment, particularly when prematurity, poor postnatal growth, intestinal disease, prolonged parenteral nutrition, or high gastrointestinal losses are present. However, routine zinc screening or supplementation for all infants with fetal growth restriction is not currently supported by definitive neonatal guidelines and should remain individualized [7, 19].

Zinc and breast milk

Breast milk is a species-specific source of nutrients and bioactive factors that supports infant growth and contributes to protection against infections [20]. Zinc concentration in human milk is highest in colostrum and declines during lactation. In most healthy lactating women, milk zinc concentration is relatively protected from short-term dietary variation, but severe maternal malnutrition, restrictive diets, and rare genetic defects affecting zinc transport into milk can lead to clinically relevant low zinc availability for the infant. Transient neonatal zinc deficiency has been described in exclusively breastfed infants when mammary zinc secretion is impaired, most commonly in relation to *SLC30A2* variants. This condition should be suspected in breastfed infants with periorificial or acral dermatitis, poor growth, diarrhea, or low serum zinc [21, 22]. Although zinc supplementation is generally unnecessary for healthy term breastfed infants, it may be considered in preterm, very-low-birth-weight (VLBW), or small-for-gestational-age infants when growth is suboptimal or additional risk factors for deficiency are present [7, 20, 23].

Zinc supplementation in preterm and low-birth-weight infants

Preterm and VLBW infants are vulnerable to zinc deficiency because most fetal zinc accretion occurs during the third trimester, while postnatal illness, delayed enteral feeding, limited body stores, immature absorption, and gastrointestinal or urinary losses may reduce zinc availability [7, 23]. Preventive enteral zinc supplementation in preterm infants may reduce all-cause mortality and improve short-term growth, but available evidence shows little or no effect on several common prematurity-related morbidities and provides no reliable data on long-term neurodevelopment [15, 24]. The clinical interpretation of these findings is nuanced. Some trials and meta-analyses suggest benefit for growth and selected short-term outcomes, whereas the certainty of evidence is limited by heterogeneity in gestational age, baseline intake, dose, duration, and outcome definitions [6, 24, 25]. Current practice should therefore prioritize adequate zinc provision through evidence-based enteral and parenteral nutrition, targeted supplementation in high-risk infants, and monitoring of growth, biochemical status, and safety rather than routine high-dose supplementation for all preterm infants. Current ESPGHAN-based and BAPM-endorsed neonatal guidelines support an enteral zinc intake of 2-3 mg/kg/day for preterm infants < 1.8 kg, while serum zinc assessment should be considered in infants with poor linear growth, low alkaline phosphatase, or excessive gastrointestinal losses. These should be considered nutritional intake targets rather than therapeutic doses; routine supplementation above recommended intakes is not supported in stable infants without deficiency or high ongoing losses [23, 68]. A 2025 prospective single-center cohort in very preterm/VLBW infants associated implementation of routine enteral zinc to meet recommendations with improved linear growth, but frequent low serum zinc values persisted and multicenter trials are still needed before escalating universal doses [69].

Zinc and neonatal hyperbilirubinemia

Neonatal jaundice is one of the most common neonatal conditions, occurring in a large proportion of term and preterm newborns. Although most cases are benign, severe unconjugated hyperbilirubinemia can cause acute bilirubin encephalopathy and kernicterus [26, 27]. Zinc supplementation has been proposed as an adjunct to phototherapy, rather than as an alternative to established treatment. Several studies and meta-analyses suggest that zinc supplementation combined with phototherapy may reduce serum bilirubin and/or shorten phototherapy duration, but the evidence remains limited by heterogeneity in gestational age, dose, timing, baseline bilirubin level, and study design [28, 29]. The proposed mechanism is that zinc binds bilirubin in the intestinal lumen and forms poorly absorbable complexes, thereby reducing enterohepatic recirculation and facilitating fecal excretion [29, 30]. This mechanism may also explain why the effect may be weaker or less consistent in low-birth-weight and preterm infants, in whom intestinal maturation, feeding tolerance, and enterohepatic physiology differ from those of term infants [31, 32]. The timing of administration may influence apparent efficacy, and the best response appears more likely when zinc is started early during phototherapy; however, optimal dose and timing remain uncertain [32]. The most recent meta-analysis, which included 14 randomized trials, found lower total serum bilirubin at 24-72 hours and on day 4, but with high heterogeneity, low to very-low certainty for most outcomes, no

significant reduction in phototherapy or hospital-stay duration, and no clear benefit in preterm or low-birth-weight infants. The clinical conclusion should therefore be conservative: zinc can be described as a possible adjunct under investigation, not as routine co-therapy for neonatal jaundice [70].

Zinc and the preterm brain

Zinc is involved in neurotransmission, synaptic plasticity, neuronal modulation, neurogenesis, and myelination [10]. The placenta and fetal liver contribute to zinc transfer, accretion, storage, and utilization through transporter and enzymatic pathways. Disruption of these mechanisms may reduce zinc availability during a critical phase of brain development [10]. Myelin production is partly zinc dependent, and experimental data suggest that developmental zinc deficiency may affect astrocytes, oligodendrocytes, and myelin protein profiles [33]. Brain metalloproteins and metalloproteinases are influenced by zinc and contribute to neuronal protection, extracellular matrix remodeling, and the matching of metabolic demand with developmental processes in the brain [34]. The hippocampus contains high concentrations of zinc, and zinc-dependent signaling has been linked to learning, memory, and behavior [35]. Zinc also contributes to neuronal precursor survival through pathways such as extracellular signal-regulated kinases (ERK) signaling; zinc deficiency may impair proliferation and promote apoptosis in experimental models [36]. Zinc-dependent mechanisms are also involved in the specification and maturation of selected neuronal populations, including cerebellar cell subsets [37]. Despite strong biological plausibility, clinical evidence that neonatal zinc supplementation improves long-term neurodevelopmental outcomes remains insufficient. Current reviews support the need for adequately powered trials with standardized dosing, careful assessment of baseline zinc status, and long-term follow-up [6, 10, 24]. Recent infant neuroimaging data add biological plausibility: in a small prospective cohort, higher maternal prenatal zinc intake was associated with MRI markers of neonatal brain microstructural maturation and higher cognitive scores at 14 and 24 months. This supports adequate maternal and fetal zinc nutrition, but it remains observational evidence and should not be interpreted as proof that neonatal zinc supplementation improves long-term neurodevelopment [71].

Zinc and bacterial infections

Zinc contributes to epithelial barrier integrity, innate and adaptive immune function, T-cell and NK-cell activity, and neutrophil and monocyte function [38]. In newborns and young infants, studies evaluating zinc as an adjunctive treatment for bacterial infections have produced heterogeneous results. Some trials have reported reductions in inflammatory markers, treatment failure, or mortality, whereas others have not shown significant differences in clinical outcomes [38]. The incidence and prognosis of neonatal sepsis vary widely by setting, gestational age, birth weight, organism, and case definition. Meta-analytic data including 8 randomized trials suggest that adjunctive oral zinc at 3 mg/kg twice daily, in addition to antibiotics and supportive care, may reduce mortality in young infants with sepsis; however, the benefit was less clear in analyses restricted to neonates under 1 month of age [39, 40]. UNICEF and WHO recommendations on zinc are primarily directed to maternal micronutrient strategies in high-risk settings and to the management of childhood diarrhea; they should not be extrapolated automatically to routine neonatal sepsis treatment without considering local protocols and the available evidence [9, 41]. Overall, zinc supplementation for infection-related outcomes should be considered investigational or targeted to infants with documented or strongly suspected deficiency rather than applied indiscriminately.

Zinc and bronchopulmonary dysplasia

The impact of enteral zinc supplementation on major prematurity-related morbidities such as bronchopulmonary dysplasia (BPD) remains uncertain. Available evidence has not demonstrated a consistent reduction in BPD alone [24, 42]. Combined outcomes such as death or BPD have been explored and may suggest a possible protective trend, but current data are limited and do not allow definitive conclusions. Larger, methodologically stronger studies are needed to clarify whether zinc supplementation, through antioxidant, immune, epithelial, or developmental mechanisms, can reduce respiratory complications in preterm infants [7, 24, 25, 42].

Zinc and cardiovascular and metabolic health

Experimental and clinical data support the hypothesis that zinc deficiency during prenatal

and early postnatal life may influence later cardiovascular and metabolic health [14]. This concept is consistent with the developmental origins of health and disease model, in which early nutritional and environmental exposures may program long-term cardiovascular risk [43]. Zinc deficiency may reduce nitric-oxide-dependent vascular function and alter cardiac developmental trajectories, including cardiomyocyte morphology and ventricular wall characteristics in experimental models [14, 44]. Endothelial nitric oxide synthase regulates vasodilation, platelet aggregation, and endothelial apoptosis; zinc contributes to the structure and function of nitric oxide synthase enzymes, and deficiency may impair vascular homeostasis [44]. VLBW infants followed by rapid postnatal catch-up growth may carry increased long-term cardiometabolic risk, underscoring the importance of balanced nutritional strategies rather than excessive or unmonitored supplementation [43]. Further clinical trials are needed to determine whether zinc supplementation can improve cardiovascular or metabolic outcomes in neonates, or whether its benefits are limited to correction of deficiency and support of growth [14].

Zinc and the intestine

Zinc is involved in the regulation of intestinal epithelial cells, tight junctions, mucosal repair, and immune defense. Zinc deficiency can impair barrier function, while zinc repletion may help restore epithelial integrity. For childhood diarrhea, WHO recommends zinc supplementation for 10-14 days: 20 mg/day for children older than 6 months and 10 mg/day for infants younger than 6 months. These recommendations refer to pediatric diarrhea management and should be applied cautiously in neonates, especially preterm infants [41, 45]. In neonates with intestinal disease, stomas, high gastrointestinal losses, prolonged parenteral nutrition, intestinal surgery, or post-necrotizing-enterocolitis anatomy, zinc losses may be substantial. Infants with jejunostomy or ileostomy often require higher parenteral zinc intake and close biochemical monitoring [46-48].

Zinc and skin

Zinc is an important cofactor for skin and mucosal integrity. Zinc deficiency may cause periorificial, acral, or diaper-area dermatitis in newborns and infants. Acquired zinc-deficiency dermatitis has been reported in infants receiving prolonged parenteral nutrition and in exclusively breastfed infants with low milk zinc content [21, 22, 49]. Transient neonatal zinc deficiency related to breast milk may be caused by maternal *SLC30A2* variants, which reduce zinc secretion into breast milk and can substantially lower milk zinc concentrations [21, 22]. Zinc-deficiency dermatitis in breastfed infants can be treated with oral zinc supplementation; reported doses vary, but approximately 1-3 mg/kg/day of elemental zinc is commonly used according to clinical severity and etiology, with monitoring for response and toxicity [22, 50]. Acrodermatitis enteropathica is a rare autosomal recessive disorder caused by mutations in *SLC39A4*, resulting in impaired intestinal zinc absorption. Its estimated incidence is approximately 1:500,000 newborns [50, 51]; classically, acrodermatitis enteropathica manifests after weaning because the relative bioavailability of zinc from breast milk may temporarily mitigate symptoms; formula-fed infants may present earlier [51]. Inherited acrodermatitis enteropathica requires lifelong elemental zinc supplementation, often around 3 mg/kg/day, with dose adjustment according to clinical response and serum zinc levels [50, 51]. Acquired or transient zinc-deficiency dermatitis usually responds rapidly to supplementation once the underlying cause is corrected; clinical improvement often begins within days [50]. In diaper dermatitis, one randomized study reported that preventive zinc oxide cream reduced incidence and delayed onset compared with talcum powder, supporting its barrier-protective role [52].

Zinc and autism spectrum disorder

Zinc is essential for cellular proliferation and brain development, and deficiency during early life can affect neurodevelopmental processes [12, 53]. Thus, possible consequences of zinc deficiency could be on neurodevelopment (autism spectrum disorder [ASD], attention deficit hyperactivity disorder [ADHD], depression, increased anxiety and immobility, repetitive behaviors, and altered social behaviors). Zinc may influence pathways relevant to ASD, including brain growth, neuropeptide signaling, synaptic function, neuronal transmission, and gut-brain interactions [1, 12]. Altered brain growth and connectivity are central features in several neurodevelopmental models of ASD [54]. Insulin-like growth factor 1 (IGF-

1), an important growth factor in the brain and other organs, may be influenced by zinc status. Some hypotheses therefore link zinc deficiency, IGF-1 signaling, and neurodevelopmental vulnerability [55-57]. Oxytocin and vasopressin are neuropeptides involved in social behavior and may be modulated by zinc-dependent pathways in experimental models [58-60]. Animal studies suggest that prenatal inflammatory exposure and zinc deficiency may induce autism-like behaviors, and that zinc treatment may prevent some behavioral and neurochemical alterations in selected models [61, 62]. In children with ASD, some studies have found lower zinc levels in hair, blood, or dental biomarkers compared with controls; altered zinc/copper ratios have also been associated with ASD severity in some cohorts [63-66]. However, human studies are heterogeneous and often limited by design, confounding factors, exposure assessment, and the difficulty of distinguishing cause from consequence. At present, zinc deficiency should be corrected when documented, but zinc supplementation cannot be recommended as a proven strategy to prevent or treat ASD in the absence of deficiency [67]. Zinc deficiency may be a modifiable neurodevelopmental risk factor in selected contexts, particularly during pregnancy and early infancy, but further prospective clinical studies are required before causal or preventive claims can be made [62, 65, 67].

Conclusions

Zinc is a crucial micronutrient in neonatal health, with central roles in growth, immune function, neurodevelopment, intestinal integrity, skin health, and cardiovascular and metabolic regulation. Zinc deficiency during fetal and neonatal life may contribute to several pathological conditions, including fetal growth restriction, impaired growth, infections, altered neurodevelopment, dermatitis, intestinal barrier dysfunction, and possibly later cardiometabolic vulnerability. Associations with ASD remain biologically plausible but not clinically proven. Premature and low-birth-weight infants are particularly vulnerable because of reduced third-trimester placental transfer, limited body stores, illness-related losses, and impaired intestinal absorption. Neonates with intestinal stomas, prolonged parenteral nutrition, severe systemic disease, poor postnatal growth, or exclusive breastfeeding with impaired mammary zinc secretion require particular attention. Zinc supplementation has shown promising effects in selected settings, including treatment of zinc-deficiency dermatitis, support of short-term growth in some preterm or low-birth-weight infants, reduction in diarrhea severity or duration in pediatric populations, possible reduction of mortality in young-infant sepsis, and adjunctive bilirubin reduction during phototherapy. Nevertheless, many studies remain heterogeneous in design, dosage, timing, population, and outcome definitions. Current evidence does not support indiscriminate zinc supplementation for all neonates. Further large-scale randomized clinical trials are needed to define optimal serum or plasma zinc targets, enteral and parenteral dosing strategies, safety thresholds, interactions with other trace elements, and long-term neurodevelopmental and cardiometabolic outcomes. Until stronger evidence is available, early recognition of deficiency and individualized nutritional intervention remain the most appropriate strategy, particularly in vulnerable neonatal populations.

Declaration of interest

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