A.10b Zinc supplementation

Recommendation and remarks

RECOMMENDATION A.10b (UPDATED)

Enteral zinc supplementation may be considered for human milk-fed preterm or low-birth-weight infants who are not receiving zinc from another source. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The GDG noted that the evidence on harms (decreased neurodevelopment) was uncertain due to very-low-certainty evidence and imprecision.
- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that there were limited data on the dose, timing of initiation and duration of supplementation. Based on most trials included in the evidence review, the GDG suggests a daily dose of 1–3 mg/kg per day of elemental zinc. The GDG also suggests that zinc may be initiated when enteral feeds are well established, and may be continued until the infant receives zinc from another source.

Background and definitions

Zinc is a trace element essential for physiological functions of the human body *(103)*. Zinc deficiency is associated with dysfunction in epidermal, gastrointestinal, central nervous, immune, skeletal and reproductive systems *(104,105)*. Human milk may not be able to meet the nutritional requirements of preterm or LBW infants because of their low zinc stores and catch-up growth *(104-106)*. A recent (2021) Cochrane review of enteral zinc supplementation in hospitalized preterm infants fed any type of milk (i.e. infant formula or human milk) reported that zinc supplementation reduced all-cause mortality and was associated with a probable improvement in short-term weight gain and linear growth, but had little or no effect on common morbidities of prematurity *(107)*. However, there have been no recent systematic reviews of zinc supplementation in babies born at home or in the hospital or on babies fed human milk only. The optimal dose and timing of initiation are also unclear.

Summary of the evidence

OVERVIEW	A.10b Zinc supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Zinc supplementation **Comparator** – No zinc supplementation **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg) • Dose of elemental zinc (< 3 mg/day, 3–5 mg/day and > 5 mg/day)

Effectiveness: Comparison – Zinc supplementation versus no zinc supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of 14 RCTs totalling 9940 preterm or LBW infants from 11 countries (Bangladesh, Brazil, Chile, Egypt, India, the Islamic Republic of Iran, Italy, the Republic of Korea, Nepal, Spain and the United Republic of Tanzania) *(108)*. Most infants had a birth weight of at least 1.5 kg or were born at 32 weeks' gestation or later. Among these, two large RCTs assessed the effects of zinc supplementation in a total of 2748 term LBW infants in Brazil and India. Zinc supplementation dosages across all 14 RCTs ranged from 1 mg/day up to 10 mg/day and commenced between birth and 35 days of age. Most

studies used a zinc dose of 3–5 mg/day. The mean duration of supplementation was 182 (SD 142) days and the median duration was 141 (IQR 98–183) days.

Critical outcomes

For zinc supplementation compared with no zinc supplementation, six trials reported all-cause mortality, six reported morbidity (2 reported hospitalization, 6 diarrhoea, 2 acute respiratory infection, 2 sepsis), eight reported growth outcomes (8 reported weight gain, 6 length gain, 5 head circumference) and two reported neurodevelopment (MDI and PDI [BSID-II]). (Full details are provided in GRADE Table A.11, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from six trials totalling 8801 participants suggests a decrease in all-cause mortality at latest follow-up (median 26 [IQR 14–152.1] weeks) (RR 0.73, 95% CI 0.46 to 1.16). There was a similar effect on all-cause mortality when the two trials with term LBW infants were excluded (RR 0.68, 95% CI 0.43 to 1.09; 4 trials, 7192 participants).
- **Morbidity:** Moderate-certainty evidence from six trials totalling 1947 participants suggests a decrease in diarrhoea (events) at latest follow-up (median 26 [IQR 20.1–52.1] weeks) (RR 0.81, 95% CI 0.68 to 0.97). Very-low-certainty evidence from two trials totalling 172 participants suggests a decrease in acute respiratory infection at latest follow-up (median 13 [IQR 6–20] weeks) (RR 0.32, 95% CI 0.09 to 1.17). Low-certainty evidence from two trials totalling 265 participants suggests little to no effect on sepsis at latest follow-up (median 17 [IQR 14 to 20] weeks) (RR 1.12, 95% CI 0.62 to 2.02).
- **Growth:** Moderate-certainty evidence from 8 trials totalling 798 participants suggests an increase in weight (in grams) at latest follow-up (median 22 [IQR 13.5–39] weeks) (MD 378.57, 95% CI 275.26 to 481.88). Low-certainty evidence from six trials totalling 529 participants suggests an increase in length (in centimetres) at latest follow-up (median 36.1 [IQR 20–52.1] weeks) (MD 2.92, 95% CI 1.53 to 4.31). Low-certainty evidence from five trials totalling 466 participants suggests an increase in head growth (in centimetres) at latest follow-up (median 20 [IQR 13–24] weeks) (MD 0.56, 95% CI 0.23 to 0.9).
- **Neurodevelopment:** Very-low-certainty evidence from two trials totalling 301 participants suggests a decrease in MDI (BSID-II) scores at latest follow-up (52 weeks) (MD -4.18, 95% CI -1.85 to -6.51). Very-low-certainty evidence from two trials totalling 301 participants suggests an increase in PDI (BSID-II) scores at latest follow-up (52 weeks) (MD 5.75, 95% CI -4.83 to 16.33).

Other outcomes

There was a decrease in hospitalization (at least one hospitalization) at latest follow-up (RR 0.70, 95% CI 0.24 to 2.00; 2 trials, 277 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome. For the dose of elemental zinc, no subgroup differences were seen for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. There was no specific evidence available about whether families value zinc supplements for their preterm or LBW baby or whether they find them acceptable.

Resources required and implementation considerations

Organization of care

The supplements can be provided in the health-care facility or at home. The family needs accurate information on the dose and how to administer the supplement. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Zinc supplements are often provided as either 5 mg zinc capsules that are then opened and mixed with 5 ml of water (1 mg elemental zinc per ml) or zinc-containing multinutrient syrups (5 mg elemental zinc in 120 mls) (i.e. 42 µg elemental zinc per ml). Babies are often prescribed 1–5 mls of these formulations daily. Droppers or syringes can be used to administer the supplement to the infant. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence available about the feasibility and equity of providing zinc supplements to preterm or LBW babies.

Summary of judgements

Comparison: Zinc supplementation vs no zinc supplementation (A.10b)	
Justification	• Evidence of small-to-moderate benefit: decreased mortality *(low-certainty evidence)*, decreased diarrhoea *(moderate-certainty evidence)*, decreased respiratory infection *(very-low-certainty)*, increased weight, length, head circumference *(moderate-certainty evidence)* and increased psychomotor development scores *(very-low-certainty evidence)* • Evidence on harms uncertain: decreased mental development scores *(low-certainty evidence)* • Evidence of little or no effect on sepsis *(low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Small to moderate
Harms	Unknown
Certainty	Low
Balance	Probably favours zinc supplementation
Values	Uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable