A.10 MICRONUTRIENT SUPPLEMENTATION

A.10a Iron supplementation

Recommendation and remarks

RECOMMENDATION A.10a (UPDATED)

Enteral iron supplementation is recommended for human milk-fed preterm or low-birth-weight infants who are not receiving iron from another source. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- The GDG noted that there were limited data on dose, timing of initiation and duration of iron supplementation.
- Based on most trials included in the evidence review, the GDG suggests a daily dose of 2–4 mg/kg per day of elemental iron may be initiated when enteral feeds are well established, and may be continued until the infant receives iron from another source.

Background and definitions

Iron deficiency is associated with poor growth and development outcomes in term and preterm babies *(100,101)*. Human milk may not meet the nutritional requirements of preterm or LBW infants because of their low iron stores, red blood cell expansion, catch-up growth and iatrogenic blood loss. The most recent systematic reviews of RCTs and non-randomized studies reported that enteral iron supplementation may improve haematological outcomes in preterm and LBW babies but that there was insufficient evidence to assess effects on growth and neurodevelopmental outcomes *(100,101)*. The optimal dose, optimal timing of initiation and the level and types of morbidity associated with iron supplementation were also unclear. In 2011, WHO recommended that VLBW infants fed mother's own milk or donor human milk should be given iron supplementation of 2–4 mg/kg per day starting at 2 weeks and continuing until 6 months of age *(19)*.

Summary of the evidence

OVERVIEW	A.10a Iron supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Iron supplementation **Comparator** – No iron 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)

Effectiveness: Comparison – Iron supplementation versus no iron supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of eight trials (11 publications) reporting on a total of 1093 infants from seven countries (Canada, Germany, India, the Netherlands, Sweden, the United Kingdom and the USA) *(102)*. Most trials enrolled babies with birth weight below 1.5 kg or born before 32 weeks' gestation. The trials used iron supplementation doses ranging from 1 to 7 mg/kg per day, median 2.2 (IQR 1.97–2.55) mg/kg per day. Supplementation commenced between 14 and 56 days chronological age. The mean duration of supplementation was 81 (SD 57) days and the median duration was 53 (IQR 40–98) days. One trial gave iron with multivitamin supplements and compared this with infants who received multivitamins alone. The remaining seven trials gave iron supplementation alone and compared this with placebo or no iron supplementation.

Critical outcomes

For enteral iron supplementation compared with no iron supplementation, four trials reported morbidity (4 reported sepsis, 2 necrotizing enterocolitis), five reported growth outcomes (5 reported weight, 3 length, 3 head circumference) and one reported on neurodevelopment (cognitive outcomes). No studies reported all-cause mortality. (Full details are provided in GRADE Table A.10, in the Web Supplement.)

- **Morbidity:** Very-low-certainty evidence from four trials totalling 270 participants suggests little or no effect on sepsis prevalence at latest follow-up (median 8 [IQR 8–9] weeks) (RR 1.08, 95% CI 0.56 to 2.07). Very-low-certainty evidence from two trials totalling 194 participants suggests little or no effect on necrotizing enterocolitis prevalence at latest follow-up (median 9 [IQR 8.5–9.5] weeks) (RR 1.54, 95% CI 0.69 to 3.46).
- **Growth:** Low-certainty evidence from five trials totalling 574 participants suggests an increase in weight in grams at latest follow-up (median 26 [IQR 8–36] weeks) (MD 35.31, 95% CI -64.53 to 135.15). Moderate-certainty evidence from three trials totalling 384 participants suggests an increase in length in centimetres at latest follow-up (median 26 [IQR 8–183] weeks) (MD 0.69, 95% CI 0.01 to 1.37). Low-certainty evidence from three trials totalling 385 participants suggests little or no effect on head circumference at latest follow-up (median 26 [IQR 8–183] weeks) (MD 0.09, 95% CI -0.4 to 0.21).
- **Neurodevelopment:** Very-low-certainty evidence from one trial with 199 participants suggests little or no effect on cognitive development (measured using the Wechsler Intelligence Scale for Children, fourth edition [WISC-IV]) at latest follow-up (mean 365 weeks) (RR 0.31, 95% CI 0.09 to 1.02).

Other outcomes

Moderate-certainty evidence from two trials totalling 381 participants suggests a decrease in anaemia prevalence at latest follow-up (RR 0.25, 95% CI 0.10 to 0.62). Moderate-certainty evidence from five trials totalling 506 participants suggests an increase in haemoglobin prevalence at latest follow-up (mean 26 weeks) (MD 4.79, 95% CI 2.9 to 6.69). Very-low-certainty evidence from six trials totalling 607 participants suggests little or no effect on ferritin levels at latest follow-up (median 14 [IQR 8–26] weeks) (MD 8.76, 95% CI -0.85 to 18.37). Very-low-certainty evidence from two trials totalling 238 participants suggests little or no effect on feed intolerance at latest follow-up (mean 8 weeks) (RR 1.05, 95% CI 0.49 to 2.27).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials 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 iron 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

Iron supplements are commonly provided to LBW and preterm infants as oral liquid solution. Infants are commonly prescribed 2–4 mg/kg of elemental iron per day for the prophylaxis of iron deficiency anaemia. Concentrations of 5 mg of elemental iron per millilitre of liquid are often used (e.g. 1 ml/day to a 2 kg baby will provide 2.5 mg of elemental iron per day). Droppers or syringes can be used to administer the supplement to the infant. Doses are different for the treatment of iron deficiency anaemia. 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 of providing iron supplements to preterm or LBW babies.

Summary of judgements

Comparison: Iron supplementation vs no iron supplementation (A.10a)	
Justification	• Evidence of small-to-moderate benefit: decreased anaemia, increased weight and length *(low-certainty evidence)* • No evidence of harms • Evidence of little or no effect on sepsis and necrotizing enterocolitis *(very-low-certainty evidence)*, and on weight, head circumference and neurodevelopment *(low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Small to moderate
Harms	Trivial or none
Certainty	Moderate
Balance	Favours iron supplementation
Values	No uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable