A.10f Multiple micronutrient (MMN) supplementation

Recommendation and remarks

NO RECOMMENDATION

Remark

- The GDG decided not to make a recommendation on MMN supplementation as there was no evidence of benefits or harms on any critical outcome.

Background and definitions

Many health workers advise families to give MMN supplements to human-milk-fed preterm and LBW infants *(76,123)*. The supplements commonly include A, D, E, B group vitamins, and some contain iron, zinc, folate and magnesium *(56)*. However, there has been no systematic review of the effect of MMN supplements on health and developmental outcomes in preterm and LBW infants.

Summary of the evidence

OVERVIEW	A.10f MMN supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Enteral MMN supplementation **Comparator** – No MMN 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 – MMN supplementation versus no MMN supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of the effectiveness of MMNs defined as three or more micronutrients (vitamins A, D, E, B group, iron, zinc, folate or magnesium). Two RCTs were included, which enrolled a total of 414 preterm or LBW infants from two countries (Mexico and the United Republic of Tanzania) *(126)*. The United Republic of Tanzania trial recruited 339 preterm or LBW infants. The Mexico trial recruited 75 preterm or LBW infants. The United Republic of Tanzania trial intervention was vitamin C, E, B group, folate and vitamin B12, which was compared with no MMN in the control group. The Mexico trial gave the same nutrients to the intervention group plus zinc, magnesium, vitamin D, vitamin A and iron, and compared this with vitamin A and iron in the control group. The United Republic of Tanzania trial initiated supplementation at 66 weeks of age and continued until 18 months of age, while the Mexico trial started supplementation at 3 months, continuing until 24 months of age.

Critical outcomes

For enteral MMN supplementation compared with no MMN supplementation, two trials reported growth outcomes (weight-for-height z score [WHZ], HAZ, WAZ) and one trial reported neurodevelopmental outcomes (cognition, receptive language, expressive language, fine motor, gross motor). No trials reported mortality or morbidity outcomes, and no trials reported on serious adverse events. (Full details are provided in GRADE Table A.10f, in the Web Supplement.)

- **Growth:** Low-certainty evidence from two trials totalling 398 participants suggests little or no effect on wasting (WHZ < -2 SD) at latest follow-up (mean 91 weeks) (RR 0.86, 95% CI 0.50 to 1.48). Low-certainty evidence from two trials totalling 399 participants suggests little or no effect on stunting (HAZ < -2 SD) at latest follow-up (mean 91 weeks) (RR 1.17, 95% CI 0.83 to 1.66). Low-certainty evidence from two trials totalling

396 participants suggests little or no effect on underweight (WAZ < -2 SD) at latest follow-up (mean 91 weeks) (RR 1.22, 95% CI 0.85 to 1.22). There was also little or no effect on change in WHZ, HAZ or WAZ scores from baseline to endline in the studies.

- **Neurodevelopment:** At latest follow-up, very-low-certainty evidence from one trial with 27 participants suggests little or no effect on: cognition scores (78 weeks) (MD 2.64, 95% CI -0.48 to 5.67); receptive language scores (78 weeks) (MD 1.19, 95% CI -0.33 to 2.71); expressive language scores (78 weeks) (MD 0.94, 95% CI -1.13 to 3.01); fine motor scores (78 weeks) (MD 1.03, 95% CI -1.13 to 3.19); and gross motor scores (78 weeks) (MD 1.14, 95% CI -0.56 to 2.84). All of these neurodevelopment outcomes were measured using BSID-III.

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials reporting on 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 MMN supplements for their preterm or LBW baby or 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

Common methods of providing enteral MMN supplements for preterm and LBW infants include infant multivitamin formulations (e.g. vitamins D, A, C, B group with added iron) in 30–50 ml bottles. 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 MMN supplements to preterm or LBW babies.

Summary of judgements

Comparison: MMN supplementation vs no MMN supplementation (A.10f)	
Justification	• Evidence of little or no effect on weight, length and neurodevelopment *(low- to very-low-certainty evidence)* • No evidence on other critical outcomes
Evidence-to-Decision summary	
Benefits	Unknown
Harms	Unknown
Certainty	Low to very low
Balance	Does not favour MMN supplementation
Values	Uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable