A.4 MULTICOMPONENT FORTIFICATION OF HUMAN MILK

Recommendation and remarks

RECOMMENDATION A.4 (UPDATED)

Multicomponent fortification of human milk is not routinely recommended for all preterm or low-birth-weight (LBW) infants but may be considered for very preterm (< 32 weeks' gestation) or very LBW (< 1.5 kg) infants who are fed mother's own milk or donor human milk. *(Conditional recommendation, low- to moderate-certainty evidence)*

Remarks

- The potential harm of mortality and necrotizing enterocolitis from fortification was considered by the GDG to be very uncertain due to the low quality of the included trials. The GDG also considered that the benefits of multicomponent fortifier were clinically important for the weight, length and head circumference of very preterm (< 32 weeks) or very-low-birth-weight (VLBW) (< 1.5 kg) infants. Thus, the GDG decided not to routinely recommend multicomponent fortifier for all preterm or LBW infants and suggested that fortification may be considered for very preterm or VLBW infants. This 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 type of fortifier used in the studies. Based on most trials included in the evidence review, the GDG suggests that commercially available multicomponent fortifiers specifically formulated for preterm infants may be considered.
- The GDG also noted that there were limited data on the timing of initiation and duration of fortification in the studies. The GDG suggests that the initiation and duration of multicomponent fortification should be based on clinical judgement.
- Mothers should also be encouraged and supported before and after birth to provide their own breast-milk (including colostrum) for their infants.

Background and definitions

Commercially available multicomponent fortifiers for infant human milk feeding can be human or animal (often cows' milk) protein based, and contain carbohydrate, fat, protein, multivitamins, iron, zinc, calcium and phosphorous in varying amounts *(56,73)*. They are provided as liquid or powder and mixed with mother's own or donor human milk *(74,75)*. Some health workers advise families to add multicomponent fortifier to human milk feeds for preterm and LBW infants with the intent to increase nutrient accretion *(76,77)*. However, there are concerns that multicomponent fortifiers are associated with adverse events such as feed intolerance and necrotizing enterocolitis *(56)*. WHO guidelines in 2011 recommended against the use of multicomponent fortifiers for all preterm and LBW babies but to use them for very-low-birth-weight (VLBW) babies (< 1.5 kg) or very preterm babies (< 32 weeks' gestation) who fail to gain weight *(19)*. There have been new trials since that time.

Summary of the evidence

OVERVIEW	A.4 Multicomponent fortification of human milk
PICO	**Population** – Preterm or LBW infants **Intervention** – Human milk with multicomponent fortifier (human derived or non-human derived) **Comparator** – Human milk without multicomponent fortifier **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) • Type of fortifier (human milk protein based, non-human milk protein based)

Effectiveness: Comparison – Multicomponent fortification versus unfortified breast-milk

Sources and characteristics of the evidence

The effectiveness evidence was derived from a 2019 Cochrane review of 18 small trials totalling 1456 preterm infants *(78)*. An updated search conducted on 1 October 2021 located no new trials. All trials were conducted in specialist paediatric hospitals, typically in NICUs. The trials were conducted in 11 countries (Brazil, Canada, Denmark, Egypt, India, Italy, Oman, South Africa, Sweden, the United Kingdom and the USA). Babies were mostly very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg).

Trials used a range of different "base" milks to feed the infants which were identical in the intervention and the control arms. Six trials used only mother's own milk, one trial used only donor human milk, seven trials used a mixture of mother's own milk and donor milk, and four trials used a mixture of mother's own milk, donor milk and preterm formula. Participants received the intervention once they were tolerating a specified quantity of milk feeding, typically at least 100 ml/kg per day, or when receiving "full" enteral feeds, typically 150 ml/kg per day.

In the intervention arm in all trials, multicomponent fortifier was mixed into the base milk and was provided according to the manufacturer's specifications. Fourteen trials used a commercially available, bovine-milk-based, powdered preparation and four trials used preterm formula powder as the multicomponent fortifier. No trials used human-milk-derived fortifier. The fortifier was provided until a prespecified body weight was attained (most commonly, 1.8–2.0 kg), until a prespecified PMA (most commonly 34–36 weeks) or until discharge home from hospital.

In the control arm, eight trials gave infants multiple supplements (i.e. multivitamins, iron, zinc, calcium and phosphorus) in similar quantities to the nutrients in multicomponent fortifier, five trials gave infants only vitamin D, and five trials gave no supplements at all. No trials gave infants additional carbohydrate or protein in the control arm.

Critical outcomes

For multicomponent fortification compared with unfortified breast-milk, two trials reported all-cause mortality, 13 reported morbidity (13 reported necrotizing enterocolitis), 14 reported growth (14 reported weight gain, 10 length gain, 11 head growth) and 1 reported neurodevelopment (Mental Development Index [MDI, BSID-II] and Psychomotor Development Index [PDI, BSID-II]). (Full details are provided in GRADE Table A.4, in the Web Supplement.)

- **Mortality:** Very-low-certainty evidence from two trials totalling 375 participants suggests an increase in all-cause mortality by discharge (RR 2.33, 95% CI 0.16 to 34.76).
- **Morbidity:** Low-certainty evidence from 13 trials totalling 1110 participants suggests an increase in necrotizing enterocolitis by hospital discharge (RR 1.37, 95% CI 0.72 to 2.63).
- **Growth:** Low-certainty evidence from 14 trials totalling 951 participants suggests an increase in weight gain (in grams per kilogram per day) by hospital discharge (MD 1.76, 95% CI 1.30 to 2.22). Low-certainty evidence from 10 trials totalling 741 participants suggests an increase in length gain (in centimetres per week) by hospital discharge (MD 0.11, 95% CI 0.08 to 0.15). Moderate-certainty evidence from 11 trials totalling 821 participants suggests an increase in head growth (in centimetres per week) by hospital discharge (MD 0.06, 95% CI 0.03 to 0.08).
- **Neurodevelopment:** Moderate-certainty evidence from one trial with 245 participants suggests little or no effect on MDI (BSID-II) by 18 months of age (MD 2.20, 95% CI -3.35 to 7.75). Moderate-certainty evidence from one trial totalling 245 participants suggests little or no effect on PDI (BSID-II) by 18 months of age (MD 2.40, 95% CI -1.90 to 6.70).

Other outcomes

There was little or no effect on length of hospital stay in weeks (MD -0.07, 95% CI -0.35 to 0.21; 6 trials, 526 infants), or feed intolerance (RR 1.05, 95% CI 0.65 to 1.67; 7 trials, 453 infants).

Subgroup analyses

The effect of gestational age and birth weight and type of fortifier could not be assessed as there were insufficient studies.

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)*. No other specific evidence was located about whether families value fortified feeds rather than unfortified feeds for their preterm or LBW baby, or find fortified feeds more or less acceptable than unfortified feeds.

Resources required and implementation considerations

Organization of care

Health-care facilities can provide multicomponent fortifier for preterm or LBW infants.

Infrastructure, equipment and supplies

The main commodity required is the fortifier, which should be a standard, nationally approved, multicomponent fortifier specially formulated for preterm or LBW infants. Commonly used fortifiers have similar amounts of carbohydrate, protein and micronutrients. Facilities for expressing breast-milk are also needed, as are facilities for the safe mixing of fortifier into expressed breast-milk. Supplies are also needed for cup or gastric tube feeding.

Workforce, training, supervision and monitoring

Health workers at all levels can provide support to mothers and families. Standardized packages are needed for training, supervision and monitoring.

Feasibility and equity

There was no specific evidence on the feasibility and equity of providing multicomponent fortifier for preterm or LBW infants.

Summary of judgements

Comparison: Multicomponent fortification vs unfortified breast-milk (A.4)	
Justification	In trials where most participants are very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg): • Evidence of small benefits: increase in in-hospital weight, length and head circumference *(moderate- to low-certainty evidence)* • Evidence on harms uncertain: mortality *(very-low-certainty evidence)*, necrotizing enterocolitis *(low-certainty evidence)* • Evidence of little or no effect on neurodevelopment *(moderate-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Small
Harms	Unknown
Certainty	Low
Balance	Varies
Values	Uncertainty or variability about outcomes
Acceptability	Unknown
Resources	Low to moderate
Feasibility	Varies
Equity	Not equitable