

A.5 PRETERM FORMULA

Recommendation and remarks

RECOMMENDATION A.5 (UPDATED)

When mother's own milk and donor human milk are not available, nutrient-enriched preterm formula may be considered for very preterm (< 32 weeks' gestation) or very low-birth-weight infants. *(Conditional recommendation, low-certainty evidence)*

Remarks

- 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 was not able to recommend a particular type of preterm formula. Based on most trials included in the evidence review, the GDG suggests that commercially available nutrient-enriched formulas specifically formulated for preterm infants may be considered.
- There was insufficient evidence to make a recommendation for infants who were born at 32–36 weeks' gestation or with birth weight of 1.5–2.4 kg. For these infants, the GDG considered that standard term formula or nutrient-enriched preterm formula may be considered, depending on clinical judgement.
- The GDG also noted that there was limited information on the timing of initiation and duration of preterm formula in the studies. The GDG suggests initiation and duration 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

If human milk is not available, then preterm and LBW infants need to be given infant formula in the first six months after birth (56). Some studies suggest that feeding preterm infants with nutrient-enriched formula (or preterm formula) rather than formula developed for term infants (also called term formula, or non-nutrient-enriched formula) might increase

nutrient accretion, growth and neurodevelopmental outcomes (76,79,80). Preterm formula often has energy content over 72 kcal/100 ml and protein content over 1.7 g/100 ml (56,81). Term formula milks have varying energy and protein content, usually below these values (56,81). In 2011, WHO did not recommend preterm formula for feeding preterm and LBW infants (19).

Summary of the evidence

OVERVIEW	A.5 Preterm formula
PICO	<p>Population – Preterm or LBW infants</p> <p>Intervention – Nutrient-enriched formula (or preterm formula)</p> <p>Comparator – Non-nutrient-enriched formula (or term formula)</p> <p>Outcomes – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up</p>
Timing, setting, subgroups	<p>Timing of the intervention – Birth to 6 months of age</p> <p>Setting – Health-care facility or home in any country or setting</p> <p>Subgroups</p> <ul style="list-style-type: none"> • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Preterm formula versus term formula

Sources and characteristics of the evidence

The effectiveness evidence was derived from a 2019 Cochrane systematic review of seven trials including 590 infants (81). An updated search conducted on 1 September 2021 located no new trials. The trials

were undertaken during the 1970s and 1980s in neonatal units in South Africa, Thailand, Türkiye, the United Kingdom and the USA. All infants were clinically stable preterm infants. Most were very low birth weight (< 1.5 kg). Few participants were extremely preterm (< 28 weeks), extremely low birth weight (< 1.0 kg) or growth restricted. The

trials excluded infants with congenital anomalies, or respiratory, gastrointestinal or neurological problems.

Preterm formula was defined in the systematic review as a formula with both energy content over 72 kcal/100 ml and protein content over 1.7 g/100 ml and term formula was defined as a formula with both energy content below 72 kcal/100 ml and protein content below 1.7 g/100 ml. In six trials, the formula was the sole diet while in one trial the formula was used in addition to human milk. The milk feeds were started when infants were clinically stable and able to tolerate enteral feeds in all trials. Trial participants continued to receive the intervention or control formula for two weeks or until they reached 2.0 kg. The target volume of milk intake for both groups was 150–180 ml/kg per day.

Critical outcomes

For preterm formula compared with term formula, two trials reported all-cause mortality, three reported morbidity (3 reported necrotizing enterocolitis), five reported growth (6 reported weight gain, 5 length gain, 5 head circumference) and two reported neurodevelopment (both reported MDI and PDI). (Full details are provided in GRADE Table A.5, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from two trials totalling 424 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 1.12, 95% CI 0.65 to 1.93).
- **Morbidity:** Low-certainty evidence from three trials totalling 489 participants suggests a decreased risk of necrotizing enterocolitis by hospital discharge (RR 0.72, 95% CI 0.41 to 1.25).
- **Growth:** Low-certainty evidence from six trials totalling 440 participants suggests an increase in weight gain (in grams per kilogram per day) by hospital discharge (MD 2.43, 95% CI 1.60 to 3.26). Low-certainty evidence from five trials totalling 386 participants suggests little or no effect on length gain (in millimetres per week) by hospital discharge (MD 0.22, 95% CI -0.70 to 1.13). Low-certainty evidence from five trials totalling 399 participants suggests an increase in head circumference gain (in millimetres per week) by hospital discharge (MD 1.04, 95% CI 0.18 to 1.89).
- **Neurodevelopment:** Moderate-certainty evidence from two trials totalling 310 participants suggests

an increase in MDI (BSID-II) at 18 months (MD 2.81, 95% CI -1.44 to 7.06). Low-certainty evidence from two trials totalling 310 participants suggests an increase in PDI (BSID-II) at 18 months (MD 6.56, 95% CI 2.87 to 10.26).

Subgroup analyses

For the analysis by gestational age and birth weight, differences for all critical outcomes 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 preterm formula rather than term formula for their preterm or LBW baby, or find preterm formula more or less acceptable than term formula.

Resources required and implementation considerations

Organization of care

Health workers and staff at other care facilities can provide preterm (nutrient-enriched) formula for preterm or LBW infants.

Infrastructure, equipment and supplies

The main commodity required is the preterm formula, which should be a standard, nationally approved formula, specially formulated for preterm or LBW infants. Facilities are needed for safe reconstitution of preterm formula. 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 preterm formula for preterm or LBW infants.

Summary of judgements

Comparison: Preterm formula vs term formula (A.5)

Justification	In trials where most participants are very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg): <ul style="list-style-type: none">• Evidence of small benefits: increased in-hospital weight, head circumference, neurodevelopment (<i>low-certainty evidence</i>)• No evidence of harms• Evidence of little or no effect on mortality and necrotizing enterocolitis (<i>low-certainty evidence</i>)
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Evidence-to-Decision summary

Desirable	Small
Undesirable	Trivial or none
Certainty	Low
Balance	Probably favours preterm formula
Values	No uncertainty or variability about outcomes
Acceptability	Varies
Resources	Moderate
Feasibility	Probably not feasible
Equity	Probably not equitable