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[Intervention Review]

# Formula versus donor breast milk for feeding preterm or low birth weight infants

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## ABSTRACT

### Background

When sufficient maternal breast milk is not available, alternative forms of enteral nutrition for preterm or low birth weight (LBW) infants are donor breast milk or artificial formula. Donor breast milk may retain some of the non-nutritive benefits of maternal breast milk for preterm or LBW infants. However, feeding with artificial formula may ensure more consistent delivery of greater amounts of nutrients. Uncertainty exists about the balance of risks and benefits of feeding formula versus donor breast milk for preterm or LBW infants.

### Objectives

To determine the effect of feeding with formula compared with donor breast milk on growth and development in preterm or low birth weight (LBW) infants.

### Search methods

We used the Cochrane Neonatal search strategy, including electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 6), Ovid MEDLINE, Embase, and the Cumulative Index to Nursing and Allied Health Literature (until 8 June 2017), as well as conference proceedings and previous reviews.

### Selection criteria

Randomised or quasi-randomised controlled trials (RCTs) comparing feeding with formula versus donor breast milk in preterm or LBW infants.

### Data collection and analysis

Two review authors assessed trial eligibility and risk of bias and extracted data independently. We analysed treatment effects as described in the individual trials and reported risk ratios (RRs) and risk differences (RDs) for dichotomous data, and mean differences (MDs) for continuous data, with respective 95% confidence intervals (CIs). We used a fixed-effect model in meta-analyses and explored potential causes of heterogeneity in subgroup analyses. We assessed the quality of evidence for the main comparison at the outcome level using "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) methods.

### Main results

Eleven trials, in which 1809 infants participated in total, fulfilled the inclusion criteria. Four trials compared standard term formula versus donor breast milk and seven compared nutrient-enriched preterm formula versus donor breast milk. Only the four most recent trials

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used nutrient-fortified donor breast milk. The trials contain various weaknesses in methodological quality, specifically concerns about allocation concealment in four trials and lack of blinding in most of the trials.

Formula-fed infants had higher in-hospital rates of weight gain (mean difference (MD) 2.51, 95% confidence interval (CI) 1.93 to 3.08 g/kg/day), linear growth (MD 1.21, 95% CI 0.77 to 1.65 mm/week) and head growth (MD 0.85, 95% CI 0.47 to 1.23 mm/week). We did not find evidence of an effect on long-term growth or neurodevelopment. Formula feeding increased the risk of necrotising enterocolitis (typical risk ratio (RR) 1.87, 95% CI 1.23 to 2.85; risk difference (RD) 0.03, 95% CI 0.01 to 0.06).

The GRADE quality of evidence was moderate for rates of weight gain, linear growth, and head growth (downgraded for high levels of heterogeneity) and was moderate for neurodevelopmental disability, all-cause mortality, and necrotising enterocolitis (downgraded for imprecision).

### Authors' conclusions

In preterm and LBW infants, feeding with formula compared with donor breast milk, either as a supplement to maternal expressed breast milk or as a sole diet, results in higher rates of weight gain, linear growth, and head growth and a higher risk of developing necrotising enterocolitis. The trial data do not show an effect on all-cause mortality, or on long-term growth or neurodevelopment.

## PLAIN LANGUAGE SUMMARY

### Formula versus donor breast milk for feeding preterm or low birth weight infants

#### Review question

When a mother's own breast milk is not available, does feeding preterm or low birth weight infants with formula rather than donor breast milk affect digestion and growth and the risk of severe bowel problems?

#### Background

Preterm infants often find artificial formula more difficult to digest than human milk, and concerns exist that formula could increase the risk of severe bowel problems. If preterm infants are fed with donor breast milk (when a mother's own breast milk is insufficient or unavailable), rather than an artificial formula, this might reduce the risk of these problems. Donor breast milk, however, is more expensive than many formulas, and may not contain sufficient amounts of key nutrients to ensure optimal growth for preterm or low birth weight infants. Given these concerns, we have reviewed all of the available evidence from clinical trials that compared formula versus donor breast milk for feeding preterm or low birth weight infants.

#### Study characteristics

In searches up to June 2017, we found 11 completed trials (including more than 1800 infants). Most trials, particularly those trials conducted more recently, used reliable methods.

#### Key results

The combined analysis of data from these trials shows that feeding with formula increases rates of growth during the hospital stay, but is associated with a higher risk of developing the severe gut disorder called 'necrotising enterocolitis'. There is no evidence of an effect on survival or longer-term growth and development.

#### Conclusions

The currently available evidence suggests that feeding preterm infants with artificial formula (rather than donor breast milk when mother's own breast milk is not available) is associated with faster rates of growth, but with a near-doubling of the risk of developing necrotising enterocolitis. Further, larger trials could provide stronger and more precise evidence to help clinicians and families make informed choices about this issue. Currently, five such trials (including more than 1200 infants) are ongoing internationally, and we plan to include the data from these trials in this review when these become available.