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WHO

OPTIMAL FEEDING OF LOW-BIRTH-WEIGHT INFANTS: TECHNICAL REVIEW

# Optimal feeding of low-birth-weight infants

## TECHNICAL REVIEW

World Health Organization

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## TECHNICAL REVIEW

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# Abbreviations

| | |
|---|---|
| AGA | Appropriate for gestational age |
| CI | Confidence interval |
| CMV | Cytomegalovirus |
| DBM | Drip breastmilk |
| EBF | Exclusive breastfeeding |
| EBM | Expressed breastmilk |
| ERSL | Estimated renal solute load |
| FAO | Food and Agriculture Organization |
| HIV | Human immunodeficiency virus |
| HR | Hazard ratio |
| IDA | Iron-deficiency anaemia |
| IQ | Intelligence quotient |
| IU | International units |
| IUGR | Intrauterine growth restriction/retardation |
| KMC | Kangaroo mother care |
| LBW | Low birth weight |
| MD | Mean difference |
| MTCT | Mother-to-child transmission of HIV |
| NCHS | National Centers for Health Statistics |
| OR | Odds ratio |
| PRSL | Potential renal solute load |
| RCT | Randomized controlled trial |
| RD | Risk difference |
| RNI | Recommended nutrient intake |
| RR | Relative risk |
| SGA | Small for gestational age |
| TPN | Total parenteral nutrition |
| UNICEF | United Nations Children's Fund |
| VLBW | Very low birth weight |
| WHO | World Health Organization |
| WMD | Weighted mean difference |
| Z-SCORE | Standard deviation score |

# Executive summary

Low birth weight (LBW) has been defined by the World Health Organization (WHO) as a weight at birth less than 2500 grams. The global prevalence of LBW is 15.5%, which means that about 20.6 million such infants are born each year, 96.5% of them in developing countries (*1*). There is significant variation in LBW incidence rates across the United Nations regions, with the highest incidence in South-Central Asia (27.1%) and the lowest in Europe (6.4%).

Low birth weight can be a consequence of pre-term birth (i.e. before 37 completed weeks of gestation), or due to small size for gestational age (SGA, defined as weight for gestation <10th percentile), or both. In addition, depending on the birth weight reference used, a variable but small proportion of LBW infants are born at term and are not small for gestational age. Intrauterine growth retardation, defined as a slower than normal rate of fetal growth, is usually responsible for SGA. Low birth weight thus defines a heterogeneous group of infants: some are born early, some are born at term but are small for gestational age, and some are both born early and small for gestational age.

It is generally recognized that being born with a low birth weight is a disadvantage for the infant. Pre-term birth is a direct cause of 27% of the 4 million neonatal deaths that occur globally every year (*2*). Pre-term birth and SGA are also important indirect causes of neonatal deaths. Low birth weight directly or indirectly may contribute up to 60–80% of all neonatal deaths (*2*). LBW infants are at higher risk of early growth retardation, infectious disease, developmental delay and death during infancy and childhood (*3*, *4*).

Countries can substantially reduce their infant mortality rates by improving the care of low birth weight infants. Experience from both developed and developing countries has clearly shown that appropriate care of LBW infants, including feeding, temperature maintenance, hygienic cord and skin care, and early detection and treatment of infections can substantially reduce mortality in this highly vulnerable group. Interventions to improve feeding are likely to improve the immediate and longer-term health and wellbeing of the individual infant and to have a significant impact on neonatal and infant mortality levels in the population. Better feeding of pre-term babies was one of the first interventions in the 1960s in the UK and was associated with reduced case fatality for pre-term babies in hospitals before the advent of intensive care (*5*). Community-based studies from India have shown that improved care of LBW infants can substantially improve their survival (*6–8*).

This review summarizes the evidence on feeding LBW infants and serves as the basis for the development of guidelines on feeding LBW infants in developing countries. Systematic reviews, randomized controlled trials, observational studies and descriptive studies were examined. The information was stratified into key sections (nutrition, feeding methods, feeding schedules, support and monitoring). Key questions and evidence were considered for each section and summarized. The following outcomes were considered:

- Mortality
- Severe morbidity
- Neurodevelopment
- Growth
- Other outcomes (e.g. anaemia, exclusive breastfeeding rates, feed tolerance, etc.).

Studies from developing and developed countries that included infants with a birth weight less than 2500 g or gestation less than 37 weeks were considered for inclusion in this review. Studies were classified into the following three groups based on the infant's gestational age and (where this was not available) on birth weight: (*i*) gestational age under 32 weeks or birth weight under 1500 g, (*ii*) gestational age of 32–36 weeks or birth weight of 1500–1999 g, and (*iii*) term infants with a birth weight of 2000–2499 g. These infants are considered by many experts to be distinct risk groups requiring different specialized management (*9–12*). It was not possible to present the findings of most studies separately for pre-term infants who were appropriate for gestational age (AGA) from those who were small size for gestational age (SGA).

## Findings of the review

### What to feed

#### Choice of milk

***Breastfeeding or mother's own expressed milk.*** There is strong and consistent evidence that feeding mother's own milk to pre-term infants of any gestation is associated with a lower incidence of infections and necrotising enterocolitis, and improved neurodevelopmental outcome as compared with formula feeding. Feeding unsupplemented mother's own milk to pre-term infants <1500 g resulted in slower weight and length gains, but the implications of this slower growth are unclear and there is not enough evidence to assess if it increased the risk of malnutrition. Long-term beneficial effects of breastfeeding on blood pressure, serum lipid profile or pro-insulin levels have also been reported for pre-term infants. There are limited data on most outcomes in term LBW infants; the available data suggest that improved infection and neurodevelopmental outcomes associated with feeding mother's milk in pre-term infants are also seen in this group.

***Donor human milk.*** The available data indicate that feeding with donor human milk rather than standard or pre-term infant formula to LBW infants of <32 weeks gestation reduces the incidence of necrotising enterocolitis. The data are insufficient to conclude if there are neurodevelopmental advantages. Growth is slower in the short term in the infants fed donor human milk, but there are insufficient data to assess the effects on long-term growth outcomes. It should be noted that many of the identified studies used drip milk (i.e. breastmilk that drips from the opposite breast while breastfeeding) rather than the recommended expressed donor milk. Although there is limited evidence, it can be assumed that the findings are similar in infants of 32–36 weeks gestation. There are no data on outcomes in the subgroup of term LBW infants.

***Pre-term infant formula.*** Infants of <32 weeks gestational age who were fed pre-term infant formula had higher psychomotor developmental scores at 18 months of age than those fed standard infant formula. Although there was no overall effect observed in these children at 7½–8 years of age, the verbal intelligence quotient (IQ) scores were higher in the pre-term infant formula group among boys. Pre-term formula increases growth during the neonatal period but this is not sustained during later infancy and childhood. No long-term benefits (e.g. blood pressure, serum lipid profile or pro-insulin) have been found. There are insufficient data to draw any conclusions for pre-term infants of 32–36 weeks gestational age or for term LBW infants.

## Optimal duration of exclusive breastfeeding

Overall there is no evidence to recommend a different duration of exclusive breastfeeding for pre-term or term LBW infants than for infants who are not low birth weight. Limited available data from industrialized countries suggest that early supplementation of breastfeeding (at about 3 months of age) with a high calorie diet in pre-term infants may marginally increase linear growth and haemoglobin levels. No data are available for other key outcomes. Among term LBW infants, the available evidence from two trials suggests that exclusive breastfeeding for 6 months, compared with 4 months, had no deleterious impact on neurodevelopment, growth, or haemoglobin levels, if it was accompanied by iron supplementation.

## Human milk supplementation

***Vitamin D.*** There is some evidence of reduced linear growth and increased risk of rickets in babies with a birth weight <1500 g fed unsupplemented human milk. There seems to be no consistent benefit of increasing the intake of vitamin D from the usually recommended 400 IU per day. There are no clinical trial data on the effect of vitamin D on key clinical outcomes in infants with a birth weight >1500 g.

***Phosphorus and calcium.*** There is some evidence that phosphorus and calcium supplementation reduces the risk of metabolic bone disease in pre-term infants and leads to short-term increases in bone mineralization in infants with a birth weight of <1500 g. There are no data on the effect of phosphorus and calcium supplementation on key clinical outcomes in infants with a birth weight >1500 g.

***Iron.*** Iron supplementation, started at 6–8 weeks of age in LBW infants, is effective in preventing anaemia during infancy. There is some evidence that anaemia is common in LBW infants fed unsupplemented human milk even at 8 weeks of age. There is also some evidence to suggest that iron supplementation, started at 2 weeks of age, may prevent this early anaemia in infants with birth weights <1500 g. However, there are insufficient data on the safety of iron supplementation during the first two months of life. There are no data on the effects of iron supplementation on mortality, common childhood illnesses or neurodevelopment in LBW infants.

***Vitamin A.*** No conclusions can be made about the benefits of early vitamin A supplementation of LBW infants. Findings from a single large trial suggest that vitamin A (50,000 IU in one or two divided doses) during the first days of life may have a survival advantage, particularly in infants with birth weights <2000 g.

***Zinc.*** There are no data on the effect of zinc on key clinical outcomes in pre-term infants. Data from two trials in developing countries suggest that term LBW infants in developing countries may have lower mortality and morbidity if they receive zinc supplementation. There seems to be little evidence that zinc supplementation in these infants improves neurodevelopment or affects growth.

***Multicomponent fortifier.*** In infants of <32 weeks gestation, there is evidence that use of multicomponent fortifier leads to short-term increases in weight gain, linear growth, head growth and bone mineralization. There are insufficient data to evaluate the long-term neurodevelopmental and growth outcomes, although there appears to be no effect on growth beyond one year of age. Use of multicomponent fortifiers does not appear to be associated with increased risk of mortality or necrotizing enterocolitis, although the small number of infants and the large amount of missing data in the studies reduce confidence in this conclusion. Also, in the largest trial undertaken there was a significant increase in the incidence of infection among infants receiving the fortifier. There are no data examining the efficacy of multicomponent fortifier in infants of 32–36 weeks gestation or in term LBW infants.

## How to feed

### Feeding methods

***Cup feeding compared with bottle feeding.*** In pre-term infants, cup feeding leads to higher rates of full (exclusive or predominant) breastfeeding, compared with bottle feeding at the time of discharge from hospital. Cup feeding was also associated with greater physiological stability, e.g. lower risk of bradycardia or desaturation, than bottle feeding. No data are available for term LBW infants. When cup feeding is correctly done, i.e. with the infant upright and the milk is not poured into the mouth, there is no evidence that there is an increased risk of aspiration.

***Nasogastric compared with orogastric feeding.*** Physiological data show that nasogastric tubes increase airway impedance and the work of breathing in very pre-term infants, which is supported by clinical data showing an increased incidence of apnoea and desaturation.

***Bolus compared with continuous intragastric feeding.*** Bolus feeding refers to a calculated amount of feed given intermittently every 1–4 hours by a nasogastric or orogastric tube. In infants of <32 weeks gestation, there is some evidence that bolus feeding can reduce the time to full enteral feeding, but no conclusions can be made about other advantages or disadvantages. A disadvantage of continuous feeding of expressed breastmilk is that fat can separate and stick to the syringe and tubes. There are physiological data which show that duodenal motor responses and gastric emptying is enhanced in infants of 32–35 weeks gestation given continuous intragastric feeding. There are no trial data comparing clinical outcomes associated with continuous or bolus intragastric feeding in infants of 32–36 weeks gestation or in term LBW infants.

## Feeding progression

***Trophic feedings or minimal enteral nutrition.*** Trophic feeding or minimal enteral nutrition refers to intragastric milk feeds in the first few days of life in sub-nutritional quantities, e.g. 5–10 ml/kg/day on the first day of life. A systematic review and meta-analysis of 10 randomized controlled trials (RCTs) indicate that trophic feedings in infants of <32 weeks gestation are associated with a shorter time to reach full enteral feeds and shorter duration of hospitalization. There was no significant increase in the risk of necrotising enterocolitis although the findings do not exclude an important effect. Trophic feeding is not relevant for infants of >32 weeks gestation because they usually tolerate maintenance enteral feeding from the first day of life.

***Initiation of 'maintenance' enteral feeding.*** Data are available only from two controlled studies conducted in the 1960s. One of these studies showed that infants <2250 g at birth had higher mortality if given full maintenance enteral fluids starting within 2 hours of birth as compared to those given small enteral feeds starting 12–16 hours after birth. Findings from the other study in infants of <32 weeks gestation indicated that infants given IV fluids on the first day of life had lower mortality than those who received nasogastric feeds of glucose in water or those who received no feeds or fluids. No firm conclusions can be drawn from these studies. However, it appears that very pre-term infants may benefit from avoidance of full enteral feeds on the first day of life.

***Progression of enteral feeding.*** In infants of <32 weeks gestation, faster rates of increase in feeding volumes (20–35 ml/kg/day compared with 10–20 ml/kg/day) may decrease the time to full enteral feeds and may increase weight gain. There is limited information regarding safety (broad confidence intervals for incidence of necrotising enterocolitis) and the effect on length of hospital stay. There are limited data from which to draw any conclusions about fast rates of advancement of feeding rates in infants with 32–36 weeks gestation or in term LBW infants. However, these infants are more likely to tolerate rapid feeding regimens even better than smaller more immature infants.

***Demand or scheduled feeding.*** Demand feeding may be feasible for some infants with 32–36 weeks gestation and may reduce the length of hospitalization. No data are available for infants of <32 weeks gestation and term LBW infants.

## Thermal care and support for breastfeeding

***Maternal involvement in care and feeding of LBW infants.*** Substantial benefits in terms of improved breastfeeding rates and early discharge from hospital were reported when mothers participated in the care and feeding of their LBW infants in neonatal units.

***Time of discharge from hospital.*** Several RCTs indicate that there are no adverse outcomes of early discharge, including no differences in weight gain, short-term complications and hospital readmissions, if the infants are discharged when the following criteria are met: the infant can breastfeed and maintain body temperature in an open crib, shows no evidence of clinical illness and is not losing weight, and the mother demonstrates satisfactory care-giving skills.

***Kangaroo mother care (KMC).*** In clinically stable pre-term infants with a birth weight of <2000 g, there is evidence that KMC is at least as effective as conventional care in reducing mortality. KMC may reduce infections and improve exclusive breastfeeding rates and weight gain. There are insufficient data regarding the effect of KMC in infants with birth weights <1500 g because many of these infants were excluded from the available studies as they were not considered to be clinically stable. There is preliminary evidence from resource-poor settings that KMC may be effective even in clinically unstable LBW infants including those with birth weights <1500 g. There are no data regarding the effect of KMC in term LBW infants.

***Non-nutritive sucking.*** Non-nutritive sucking may decrease the length of hospital stay in pre-term infants but has no effect on growth outcomes in preterm infants who weigh less than 1800 g at birth. Encouraging the infant to suck on the 'emptied' breast, after expression of breast milk, may result in improved breastfeeding rates at discharge and at follow-up.

***Breastfeeding counselling.*** There are few data on the effect of breastfeeding counselling among pre-term infants of <32 weeks gestation. Among pre-term infants of 32–36 weeks gestation and term LBW infants, breastfeeding counselling improves the rates of exclusive breastfeeding at 3 months. This finding is consistent with the results of a meta-analysis of 20 intervention trials in term normal birth weight infants.

***HIV and infant feeding counselling.*** No studies were located which examined the impact of HIV and infant feeding counselling of HIV-positive mothers of LBW infants or the choice of milk on key clinical outcomes.

***Drug therapy for enhancing lactation.*** The available evidence suggests that metoclopramide or domperidone increases breastmilk volume in mothers of infants of <32 weeks gestation, particularly those who were having difficulty in maintaining milk production. There are no data regarding efficacy in the mothers of infants of 32–36 weeks gestation or for term LBW infants.

## Monitoring

***Blood glucose monitoring.*** There are no studies reporting the effects of regular blood glucose monitoring on subsequent outcomes. Limited observational data indicate that recurrent and/or prolonged blood glucose levels of <2.6 mmol/l (<45 mg/dl) are likely to be associated with poorer neurodevelopment in later life.

***Growth monitoring.*** There is evidence that exact mimicry of fetal growth is not possible even in well-resourced neonatal care units in developed countries. Catch-up growth occurs after very discrepant rates of neonatal growth and is less likely to be complete in the smallest infants. The optimal timing of catch-up growth is uncertain. It is unclear if lack of rapid catch-up is associated with a higher malnutrition risk. Rapid catch-up does not appear to improve neurodevelopment. On the other hand, rapid catch-up after the first year of life may be associated with increased cardiovascular risk in later life. Although monitoring the growth of LBW infants is considered essential for appropriate management, there are no data examining the effects of growth monitoring on key clinical outcomes of LBW infants.

# Introduction

## Background

Low birth weight (LBW) is defined as a weight at birth less than 2500 g. The global prevalence of LBW is 15.5%, which means that about 20.6 million LBW infants are born each year; 96.5% of them are in developing countries (*1*). There is significant variation in LBW incidence rates across the United Nations regions:

- The highest incidence occurs in the subregion of South-Central Asia, where 27.1% of infants are born with a low birth weight. The incidence in other parts of Asia ranges from 5.9% to 15.4%.
- The incidence of LBW is 14.3% in Africa, with little variation across the region as a whole.
- Latin America and Caribbean has, on average, lower rates (10%), but in the Caribbean the level (13.7%) is almost as high as in Africa.
- About 10.5% of births in Oceania are infants with a low birth weight.
- Among the developed regions, North America averages 7.7% while Europe has the lowest regional average LBW rate at 6.4%.

Low birth weight can be a consequence of preterm birth (i.e. before 37 completed weeks of gestation) or related to a small size for gestational age (SGA, defined as weight for gestation <10th percentile), or both. In addition, depending on the birth weight reference used, a variable but small proportion of LBW infants are born at term and are not small for gestational age. Intrauterine growth retardation, defined as a slower than normal rate of fetal growth, is usually responsible for SGA. Low birth weight thus defines a heterogeneous group of infants: some are born early, some are born at term but are small for gestational age, and some are born early and are small for gestational age.

It is generally recognized that being born with a low birth weight is a disadvantage for the infant. Pre-term birth is a direct cause of 27% of the 4 million neonatal deaths that occur globally every year (*2*). Pre-term birth and SGA are also important indirect causes of neonatal deaths. Low birth weight may directly or indirectly contribute to 60–80% of all neonatal deaths (*2*). LBW infants are at higher risk of early growth retardation, infectious disease, developmental delay, and death during infancy and childhood (*3*, *4*).

Many factors affect the duration of gestation and intrauterine growth. They relate to the infant, the mother, or the physical environment and play an important role in determining the infant's birth weight:

- For the same gestational age, girls weigh less than boys, firstborn infants are lighter than subsequent infants, and twins weigh less than singletons.
- Women of short stature or with a low body mass index at conception, those who live at high altitudes, and young women have smaller babies.
- Once pregnant, the mother's lifestyle (e.g. alcohol, tobacco or drug use) and other exposures (e.g. to malaria, HIV or syphilis), or complications such as hypertension can affect intrauterine growth and development, as well as the duration of pregnancy.
- Mothers in deprived socioeconomic conditions frequently have low birth weight infants. In those settings, the mother's poor nutrition and health, high prevalence of specific and non-specific infections, inadequate care for pregnancy complications, and physically demanding work during pregnancy contribute to poor intrauterine growth.

Countries can substantially reduce their infant mortality rates by improving the care of low birth weight infants. Experience from both developed and developing countries has clearly shown that appropriate care of LBW infants, including feeding, temperature maintenance, hygienic cord and skin care, and early detection and treatment of infections can substantially reduce mortality in this highly vulnerable group. Interventions to improve feeding are likely to improve the immediate and longer-term health and wellbeing of the individual infant and to have a significant impact on neonatal and infant mortality levels in the population. Better feeding of pre-term babies was one of the first interventions in the 1960s in the UK and was associated with a reduced case fatality for pre-term babies in hospitals before the advent of intensive care (*5*). Community-based studies from India have shown that improved care of LBW infants can substantially improve their survival (*6–8*).

Feeding the LBW infant involves decisions about what milk to feed, what nutritional supplements to give, how to feed, how much and how frequently to feed, what support is needed, and how to monitor. Current guidelines on feeding the LBW infant are generally based on research in developed countries and may not be applicable in developing country settings. Unlike in developed countries, where pre-term birth is the main cause of LBW, in developing countries most LBW infants are small for gestational age (SGA). Nearly 75% of all term SGA infants in the world are born in Asia, and 20% are born in Africa (*13*, *14*). Further, many of the current feeding guidelines are not practical in resource-poor settings.

This review was designed to help the development of guidelines for feeding LBW infants, both pre-term and SGA, in first-level referral facilities in developing countries, and in the community where feasible.

## Aim

■ To summarize the evidence on feeding LBW infants in order to develop guidelines for feeding them in the first 6 months of life in developing country settings.

## Objectives

To locate, review and summarize key studies on interventions to improve the feeding of LBW infants in the first 6 months of life concerning:

- what milk to feed;
- what nutritional supplements to give;
- how to feed;
- how much and how frequently to feed;
- what support is needed for thermal care and breastfeeding;
- how to monitor feeding, fluid balance and growth.

■ To draw conclusions and make recommendations for developing guidelines, taking into account the feasibility of implementing these interventions in developing country settings.

■ To describe the development of feeding ability, fluid and nutritional requirements of pre-term and SGA infants, and the nutritional composition of human milk, human milk supplements and breastmilk substitutes.

## Target audience

This document is targeted towards neonatologists, paediatricians, nutrition experts and other health professionals who manage LBW infants, as well as public health professionals who design and evaluate healthcare programmes in developing countries. This review will form the basis of guidelines on feeding LBW infants for health professionals working in small hospitals, first-level health facilities, and communities in developing countries.

# Methods

## Inclusion criteria

### Study designs

All the available literature from both developed and developing countries was reviewed. They included published and unpublished systematic reviews, non-systematic reviews, and randomized controlled trials (RCTs); quasi-randomized trials, cohort and case-control studies were also considered.

### Definitions of participants

A *pre-term infant* is defined as an infant born before 37 weeks of gestation; a *term infant* is defined as an infant born between 37 and 41 weeks of gestation. A *small for gestational age* (SGA) infant is defined as an infant whose birth weight was less than the 10th centile for gestational age at birth, and an *appropriate for gestational age* (AGA) infant is defined as an infant whose birth weight was between the 10th centile and the 90th centile for gestational age at birth. The *corrected age* of the infant is defined as the age of the infant in weeks from the date of birth minus the number of weeks early that the infant was born, and the *chronological age* of the infant is defined as the age of the infant in weeks from the date of birth without correcting for prematurity (*9*). In general, unless otherwise specified, the chronological age of the infant is used in this document.

Studies from developing and developed countries that included infants with birth weights less than 2500 g or gestation less than 37 weeks were considered for inclusion in this review. The studies were classified into the following three groups based on the infants' gestational age and (where gestational age was not available) on birth weight: (i) gestational age under 32 weeks or birth weight less than 1500 g, (ii) gestational age of 32–36 weeks or birth weight of 1500–1999 g, and (iii) term infants with birth weights of 2000–2499 g. This classification was used as these infants are considered by many experts to be distinct risk groups requiring different levels of specialized management (*9–12*). It was not possible to present the findings of most studies separately for pre-term infants who were appropriate for gestational age (AGA) from those who were small for gestational age (SGA).

### Exposures or interventions

All nutritional exposures or interventions to improve feeding of LBW infants in the first 6 months of life were considered. These exposures and interventions were stratified into key sections: nutrition, feeding methods, feeding schedules, support, monitoring, and feeding in exceptionally difficult circumstances.

### Outcome measures

The following outcome measures were considered:

- mortality;
- severe morbidity (e.g. hospitalization rates, infectious disease incidence, necrotising enterocolitis, fractures, severe iron-deficiency anaemia with haemoglobin <7 g/dl, hypoglycaemia, adult chronic disease);
- neurodevelopment;
- malnutrition (defined as wasting or stunting: standard deviation score for weight-for-length or length-for-age <–2.0);
- other important outcomes (e.g. bone mineralization, feed tolerance, rates of any breastfeeding, and rates of exclusive breastfeeding).

Malnutrition, which is a cause of at least half of all child deaths, was included as an outcome measure rather than growth rates or weight gain because the implications of the latter on short- and long-term health and survival are still unclear. There is emerging evidence that

rapid growth during the first years of life may not be associated with improved neurodevelopment or other functional outcomes (*15–18*). However, a study by Victora et al did report a strong association between infant catch-up growth ≥0.66 SD and a lower incidence of hospital admissions in a cohort of Brazilian term SGA infants (*19*). On the other hand, rapid catch-up growth has been reported to be associated with obesity, hypertension, coronary mortality and morbidity, and impaired glucose tolerance during adult life (*20–27*). A study from Finland suggested that weight gain during infancy was associated with a reduced risk of coronary heart disease during adult life irrespective of size at birth, but after 1 year of age rapid weight gain in infants who were thin at birth was associated with an increased risk of coronary heart disease (*28*). Other studies have indicated that rapid weight gain after 2 years of age is associated with increased risk (*29, 30*).

## Search strategy for identification of studies

The search strategy included the following search terms: LBW, preterm, premature, SGA, intrauterine growth restriction/retardation (IUGR), mortality, breastfeeding, and human milk. The electronic databases used were the Cochrane database of systematic reviews of RCTs, the Cochrane controlled trials register, the Cochrane database of abstracts of reviews of effectiveness (DARE), the Cochrane neonatal collaborative review group specialized register, MEDLINE (1966 to 2005), and EMBASE (1966 to 2005). The following sources were also accessed: reference lists of articles, personal communications, technical reports, conference proceedings, review articles, books and dissertations, and experts in the field. In addition, a number of key journals were hand searched. Every effort was also made to identify relevant non-English language articles and abstracts.

## Data collection

For all studies a standardized form was used to extract relevant information from the available sources. Systematically extracted data included: study location, author, year of publication, design, participants, sample size, type of intervention or exposure, type of control group, follow-up, outcome measures, and results (including the effect of measures and tests of statistical significance, where possible). Where results adjusted for potential confounders were available, particularly for observational studies, they were used in preference to unadjusted results. Where results adjusted for potential confounders were not available, unadjusted results were used. When data were not provided, attempts were made to contact the investigators; secondary sources were used and references included.

## Data analysis

All identified studies were initially examined to assess whether they related to feeding of LBW infants. The studies were stratified according to type of intervention or exposure, study design, birth weight, and gestational age where possible. Data were tabulated and viewed descriptively. Effects were expressed as relative risks (RR) or odds ratios (OR) for categorical data, and as mean differences (MD) or weighted mean differences (WMD) for continuous data where possible.

## Level of evidence for efficacy and safety

Levels of evidence were rated according to the following scale for both efficacy and safety (US Preventative Services Task Force 1989).

I Evidence obtained from a systematic review of all relevant randomized controlled trials

II Evidence obtained from at least one properly designed randomized controlled trial

III-1 Evidence obtained from well-designed pseudo-randomized controlled trials (alternate allocation or some other method)

III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies), case-control studies, or interrupted time series with a control group

III-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group

IV Evidence obtained from case series, either post-test or pre-test and post-test

## Conclusions and implications

Level of evidence and study design were first considered. This was then followed by assessment of the limitations, internal and external validity and the wider implications of each study. Implications for guideline development were considered and the need for further research stated.

## Recommendations

Consensus statements and expert committee reports were then sought and clearly acknowledged. Experts in the field were also contacted and information about standard practice in neonatal units and health facilities was obtained. Recommendations based on the review evidence were then formulated.

## Structure of the document

Interventions are considered in chronological order, stratified into sections (nutrition, feeding methods, feeding schedules, support, monitoring, and feeding of infants of HIV-positive mothers), and key issues are considered for each intervention. Key studies are listed and described according to outcome. This is followed by conclusions and assessment of implications. Recommendations are then discussed and key implications for developing country settings.

## Limitations of this review

Most of the available evidence reviewed in this document is from studies on premature infants conducted in developed countries with low mortality rates and low rates of infectious disease because of paucity of data from developing countries. Care has been taken in extrapolating this information to developing country settings. A limitation of many of the included studies was that the results were not reported separately for the babies who were both pre-term and SGA from those who were pre-term and AGA. Further, some studies only reported the birth weights of the subjects and not their gestational ages. Regional WHO databases were not included in the search strategy and therefore some of the grey literature may have been missed.

# Results

## 1. BACKGROUND

### 1.1 Physiological principles of feeding LBW infants

#### Body composition

The composition of weight gained by the fetus varies with gestational age. About 80% of all weight gained between 24 and 28 weeks of gestation is water, but this proportion decreases to about 60% between 36 and 40 weeks. On the other hand, a greater proportion of weight gained near term is in the form of fat, increasing from about 8% during 24–28 weeks to nearly 20% during 36–40 weeks gestation (*31*) (see Figure 1.1.1).

The total body water as a percentage of body weight in the fetus decreases rapidly during the last trimester and in the first few days after birth. The decrease is because of reduction in extracellular water and somewhat compensated by a corresponding increase in intracellular water. This loss of body water after birth is responsible for the physiological weight loss seen after birth and is more pronounced in pre-term infants (5–15% of birth weight) than in term infants (3–5% of birth weight) (*32*, *33*) (see Figure 1.1.2).

#### Fluid requirements

Key physiological considerations for calculating the fluid requirements in the first week of life are:

**Figure 1.1.1** Average composition of weight gain of a reference fetus during four successive 4-week intervals (*31*)

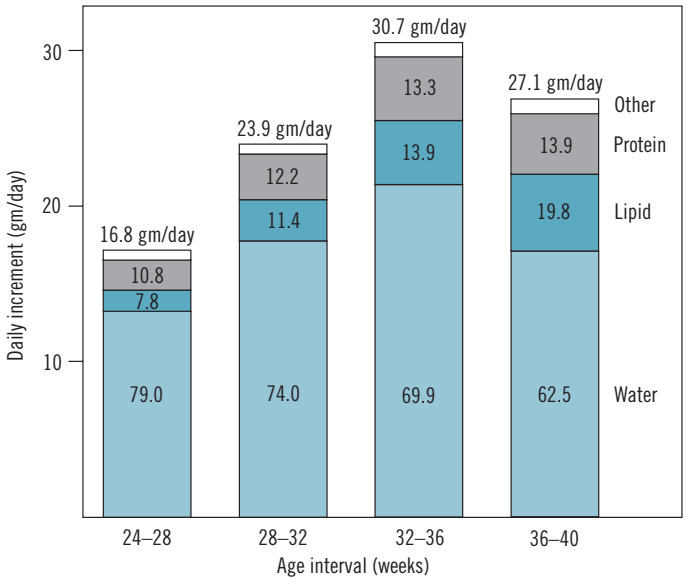
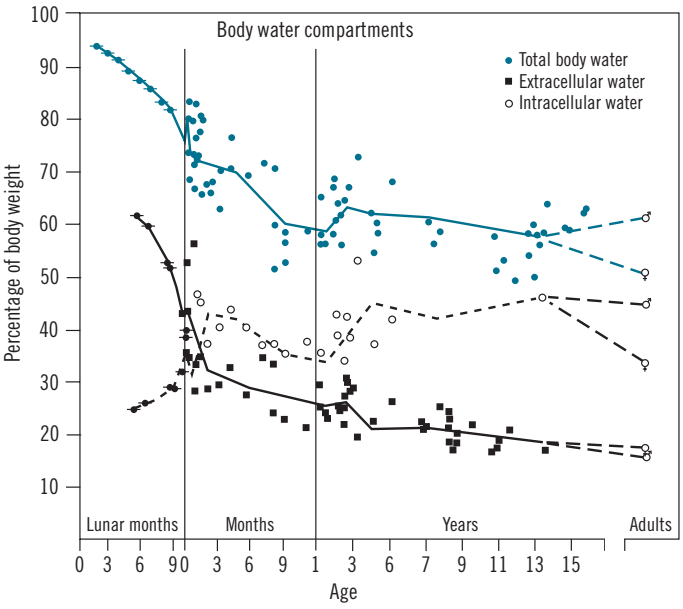



**Figure 1.1.2** Age-related changes of total body water and its compartments (intra- and extracellular) from fetal life until adolescence (*32*)



- postnatal physiological changes: 5–10 ml/kg/day water loss in the first 3–4 days for infants >1500 g and 20 ml/kg for those <1500 g (does not need to be replaced);
- insensible water loss: 20 ml/kg/day for infants >1500 g and 40–60 ml/kg/day for those <1500 g;
- urine output: 50–70 ml/kg/day for the first 3 days and 70–100 ml/kg thereafter;
- stool losses: 10 ml/kg after the first 3 days.

It is usual clinical practice therefore to provide infants weighing <1500 g with about 80 ml/kg for the first day of life and increase fluids by about 10–15 ml/kg/day to a maximum of 160 ml/kg/day by the end of the first week of life. Similarly, LBW infants >1500 g are usually given about 60 ml/kg for the first day of life and the fluid intake is increased by about 15–20 ml/kg/day to a maximum of 160 ml/kg/day by the end of the first week of life (*33–35*).

There is some evidence that further restriction of fluids for LBW infants weighing <2000 g may be beneficial but needs to be balanced against the risk of dehydration. A meta-analysis of studies comparing restricted with liberal fluid regimens demonstrated that restricted fluid regimens are associated with a reduced risk of patent ductus arteriosus, necrotising enterocolitis and death (*36*). The four studies included in the meta-analysis enrolled a total of over 400 premature infants with birth weights ranging from 750 to 2000 grams. Two of the studies examined fluid regimens during the first week of life, while the other two did so up to the end of the neonatal period. The restricted fluid regimens examined in the studies ranged from 50 to 70 ml/kg on day 1, 60–70 ml/kg on day 3, and 80–90 ml/kg on day 5. The corresponding ranges for liberal fluid regimens were 80–150 ml/kg on day 1, 120–150 ml/kg on day 3, and 140–150 ml/kg on day 5. Restricted fluid regimens were found to be associated with a lower risk of patent ductus arteriosus (RR 0.40, 95%CI 0.26, 0.63), necrotising enterocolitis (RR 0.30, 95%CI 0.13, 0.71), and death (RR 0.52, 95%CI 0.28, 0.96), but there was a non-significant trend towards increased risk of dehydration (RR 2.43, 95%CI 0.71 to 8.28).

Use of radiant warmers for temperature maintenance and phototherapy for treatment of neonatal jaundice each increased the fluid requirements by about 10 ml/kg/day (*37*, *38*).

## Energy balance

Part of energy intake is lost in the urine and stools. The remaining metabolizable energy is either expended to support basal metabolism, activity, synthesis or thermoregulation or is stored in the form of protein and fat. The total energy needs for growth are about 4–6 kcal for each gram of weight gain (*39*).

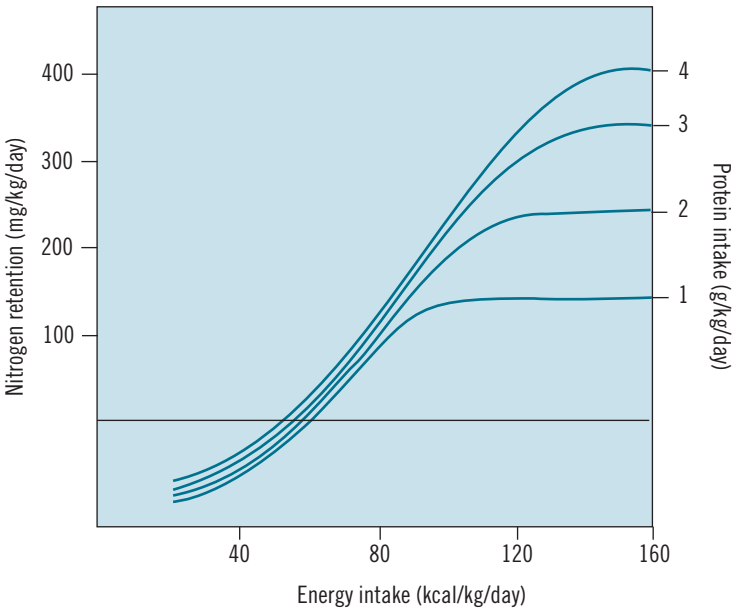
The energy needs for pre-term infants during the first week of life are about 70–80 kcal/kg/day, increase to 105–135 kcal/kg/day from the second week of life until term, and then decrease to 100–120 kcal/kg/day. Similarly, protein requirements during the first week are 1.0–3.0 g/kg/day, increase to 3.0–3.5 g/kg/day from the second week of life up to term, and then decrease to about 2 g/kg/day.

Growth in premature infants can be limited by both energy and protein intake. Protein intake is not relevant at low levels of energy intake. However, once an energy intake of 90–100 kcal/kg per day is reached, nitrogen retention can be limited if the protein intake is low (see Figure 1.1.3). Poorly growing premature infants should be first reviewed for adequacy of energy needs and if the energy needs are being met, protein supplementation could be considered. Blood urea can be used as a guide; if high, poor growth is likely to be due to inadequate energy; if low despite a high energy intake, poor growth is likely to be due to inadequate protein (*39–41*).

## Solute balance

The kidneys of a premature infant have limited ability to excrete solutes. The potential renal solute load (PRSL) is contributed by intake of protein, sodium, potassium, chloride and phosphate. A specific equation can be used to calculate the PRSL which adds sodium, potassium, chloride and phosphorus to that of nitrogen divided by 28 (PRSL = N/28 + [Na] + [K] + [Cl] + [PO4]). However, growth of the

**Figure 1.1.3** Energy intake and nitrogen retention according to protein intake in pre-term infants (*41*)




infant can reduce some of this solute load. The estimated renal solute load (ERSL) takes into account the growth of the infant and can be calculated as the potential renal solute load minus 90% of the weight gain in grams (ERSL = PRSL – [0.9 x weight gain in grams]) (*42*).

## 1.2 Nutritional requirements

Recommended nutrient intakes (RNIs) for pre-term and SGA infants have been published by a number of groups (*43–45*). The RNIs have been developed by calculating nutrient intakes that approximate the rate of growth for a normal fetus of the same gestational age without inducing metabolic stress; factorial equations; provision of idealized nutrient requirements and measurement of utilization and excretion. Published nutrient requirements for pre-term infants are shown in Box 1.2.1.

Although the published RNIs provide some indications, they cannot be used as the only basis of guidelines for feeding the LBW infant. This is because outcomes vary widely according to the basic substrate provided. In particular, the absorption and bioavailability of nutrients in different types of milk vary widely (*43–44*). This is particularly important for human milk. Bioavailability of many nutrients is higher from human milk than from infant formula or other breastmilk substitutes (*43–44*). Studies reporting clinical endpoints are more relevant for developing nutritional guidelines for LBW infants.

## 1.3 Nutritional sources for LBW infants

### HUMAN MILK

### Constituents

#### Nutrient composition

The nutrient compositions of pre-term and term human milk are displayed in Box 1.3.1. There was no information located about stratification by gestational age or birth weight. Also, no information was located which described the nutrient content of the milk of mothers who delivered SGA infants.

Breastmilk meets almost all these requirements. There may be specific need of additional minerals and vitamins for breastfed LBW infants during certain periods of life. For instance, pre-term infants of <32 weeks gestation need additional phosphorus, calcium and vitamin D from the time feeding is established until they reach term post-menstrual age. It should be noted that breastmilk has great variability in composition as seen from the standard deviations (Box 1.3.1). In general, if the breastmilk volume is high, the concentration of nutrients will be lower.

#### Anti-infective constituents

Term and pre-term human milk contains live cells (macrophages, polymorphonuclear leucocytes, T and B lymphocytes) and a range of antimicrobial factors (secretory IgA, lactoferrin, lysozyme, $B_{12}$ and folate-binding proteins, complement, fibronectin, mucin, and antiviral factors) (*47*). Human milk cells and antimicrobial factors play a major role in conferring local immunological protection to the infant's gastrointestinal tract (*47, 48*). Enzymes, antioxidants, and cellular components in human milk all improve the host defence of the LBW infant (*49*).

**BOX 1.2.1 Recommended daily nutrient intakes for pre-term infants >1000 g at birth**

| Nutrient | Birth to 7 days | Period after birth; RNI per day Stable-growing (stabilization to term) | Term to 1 year of age |
|---|---|---|---|
| **Macronutrients** | | | |
| Energy, kJ/kg (kcal/kg) | 292–334 (70–80) | 438–563 (105–135) | 417–501 (100–120) |
| Protein, g/kg | 1.0–3.0 | 3.0–3.6 | 2.2 |
| Fat, g/kg | 0.5–3.6 | 4.5–6.8 | 4.4–7.3 |
| Carbohydrate, g/kg | 5.0–20.0 | 7.5–1 5.5 | 7.5–1 5.5 |
| **Minerals** | | | |
| Calcium, mmol/kg | 1.5–2.0 | 4.0–6.0 | 6.3 mmol/d (breast fed)<br>9.4 mmol/d (formula fed) |
| Phosphorus, mmol/kg | 1.0–1.5 | 2.5–3.8 | 3.4 mmol/d (breast fed)<br>8.8 mmol/d (formula fed) |
| Magnesium, mmol/kg | 0.20–0.25 | 0.20–0.40[a] | 0.20–0.60[a] |
| Sodium,[b] mmol/kg | 1.0–3.0 | 2.5–4.0 | 2.0–3.0 |
| Chloride,[b] mmol/kg | 1.0–3.0 | 2.5–4.0 | 2.0–3.0 |
| Potassium, mmol/kg | 2.5–3.5 | 2.5–3.5 | 2.5–3.5 |
| Iron, mg/kg | 0 | 2.0–3.0[c] | 2.0–3.0[c] |
| Zinc, µmol/kg | 6.5 | 7.7–12.3 | 15.0 (estimate) |
| Copper, µmol/kg | 1.1–1.9 | 1.1–1.9 | 1. 1–1.9 |
| Selenium, µmol/kg | 0.04–0.06 | 0.04–0.06 | 0.04–0.06 |
| Chromium, nmol/kg | 1.0–1.9 | 1.0–1.9 | 1.0–1.9 |
| Manganese, nmol/kg | 10–20 | 10–20 | 10–20 |
| Molybdenum, nmol/kg | 2.0–4.0 | 2.0–4.0 | 2.0–4.0 |
| Iodine, µmol/kg | 0.20 | 0.25–0.50 | 0.25–0.50 |
| **Vitamins** | | | |
| Vitamin A, IU/kg | 700–1500 | 700–1500 | 600–1400 |
| Vitamin E, IU/kg | 6–12 | 6–12 | 6–12 |
| Vitamin K, µg/kg | 8–10 | 8–10 | 8–10 |
| Vitamin D, IU | 40–260 | 400 (800[d]) | 400 |
| Vitamin C, mg/kg | 6–10 | 6–10 | 20 |
| Vitamin $B_1$, mg/kg | 0.04–0.05 | 0.04–0.05 | 0.05 |
| Vitamin $B_2$, mg/kg | 0.36–0.46 | 0.36–0.46 | 0.05 |
| Vitamin $B_6$, mg/g of protein intake | 0.015 | 0.015 | 0.015 |
| Vitamin $B_{12}$, µg | 0.15 | 0.15 | 0.15 |
| Niacin, NE[e]/5000 U | 8.6 | 8.6 | 8.6 |
| Folate, µg | 50 | 50 | 25 |
| Biotin, µg/kg | 1.5 | 1.5 | 1.5 |
| Pantothenic acid, mg/kg | 0.8–1.3 | 0.8–1.3 | 0.8–1.3 |

[a] Amount required is higher if milk from the premature infant's mother is fortified with other minerals that may diminish the bioavailability and absorption of magnesium.

[b] In specific clinical situations, sodium and chlorine may need to be omitted for short periods.

[c] From 6 wk after birth.

[d] Amount may be increased in particular clinical syndromes.

[e] NE = niacin equivalents.

Adapted from reference number *43*.

**BOX 1.3.1 Concentration of nutrients in transitional and mature pre-term human milk compared with mature term milk**

| | Component (unit/L) | | |
|---|---|---|---|
| | Pre-term transitional (6–10 days) | Pre-term stable (22–30 days) | Term mature (> 30 days) |
| **Macronutrients** | | | |
| Energy, kcal/L | 660 ± 60 | 690 ± 50 | 640 ± 80 |
| Protein, g/L | 19 ± 0.5 | 15 ± 1 | 12 ± 1.5 |
| Fat, g/L | 34 ± 6 | 36 ± 7 | 34 ± 4 |
| Carbohydrate, g/L | 63 ± 5 | 67 ± 4 | 67 ± 5 |
| **Minerals** | | | |
| Calcium, mmol/L | 8.0 ± 1.8 | 7.2 ± 1.3 | 6.5 ± 1.5 |
| Phosphorus, mmol/L | 4.9 ± 1.4 | 3.0 ± 0.8 | 4.8 ± 0.8 |
| Magnesium, mmol/L | 1.1 ± 0.2 | 1.0 ± 0.3 | 1.3 ± 0.3 |
| Sodium, mmol/L | 11.6 ± 6.0 | 8.8 ± 2.0 | 9.0 ± 4.1 |
| Chloride, mmol/L | 21.3 ± 3.5 | 14.8 ± 2.1 | 12.8 ± 1.5 |
| Potassium, mmol/L | 13.5 ± 2.2 | 12.5 ± 3.2 | 13.9 ± 2.0 |
| Iron, mmol/L | 23 | 22 | 22 |
| Iron, mg/L | 0.4 | 0.4 | 0.4 |
| Zinc, µmol/L | 58 ± 13 | 33 ± 14 | 15 – 46 |
| Copper, µmol/L | 9.2 ± 2.1 | 8.0 ± 3.1 | 3.2–6.3 |
| Manganese, nmol/kg | 6 ± 8.9 | 7.3 ± 6.6 | 3 – 6 |
| Iodine, µmol/L | — | 1.25 | — |
| Iodine, µg/L | — | — | 70 |
| **Vitamins** | | | |
| Vitamin A, IU/L | 500–4000 | 500–4000 | 600–2,000 |
| Vitamin E, mg/L | 2.9–14.5 | 2.9–14.5 | 2–3 |
| Vitamin K, µg/L | 0.7–5.3 | 0.7–5.3 | 1.2–9.2 |
| Vitamin D, IU | 40 | 40 | |
| Vitamin D, µg/L | 0.01 | 0.01 | 0.01 |
| Vitamin $B_2$, mg/L | 0.055 mg/418 kj | 0.055 mg/418 kj | — |
| Folate, mg/L | 33 | 33 | 1.8 |

Values are mean ± SD.
From: Reference number *46*

## Amino acids

Human milk also contains many nucleotides and hormones. Approximately 20% of the total nitrogen content of human milk is represented by non-protein nitrogen, and up to 20% of the latter consists of free nucleotides (*50*). These are believed to be important in the growth and maturation of the gastrointestinal tract and in the development of neonatal immune function. Dietary nucleotides also favourably alter the bowel microflora and reduce the risk of diarrhoea. Glutamine, taurine, cysteine and inositol also serve dual roles to protect the host (*51*, *52*).

## Exocrine/endocrine components

Insulin-like growth factor-1, epidermal growth factor and transforming growth factor alpha, found in human term and pre-term milk, are believed to have trophic effects on the developing gastrointestinal tract (*53*). Human milk also contains at least 60 enzymes, including lipase, which have been shown to enhance intestinal lipolysis and improve fat absorption (*54*).

## Fatty acids

Compared to formula milk, human milk has a higher content and unique pattern of long-chain polyunsaturated fatty acids and gan-

gliosides. Long-chain polyunsaturated fatty acids are believed to be important for cell membrane synthesis, and cerebral and retinal function (*55*). Human milk gangliosides are also considered to promote neuronal development, somatic growth and the development of intestinal immunity (*56–57*).

## Types of human milk

### Mother's own milk and donor milk

Mother's own milk can be provided to the infant via breastfeeding or expression and feeding by an alternative method. Donor milk from a human milk bank is another source of human milk. This milk is screened and heat-treated and subjected to strict processing regulations. The WHO/UNICEF Global Baby-Friendly Hospital Initiative subsequently led to a revival of interest in donor milk banks. There are well functioning milk banks in a number of countries around the world including Brazil, Germany and the United Kingdom. In addition, the United Kingdom Association for Milk Banking and the Human Milk Banking Association of North America have published guidelines for the establishment and operation of human milk banks (*58*, *59*).

### Fore milk and hind milk

Fore milk is the milk that is produced as soon as the milk flow begins. Hind milk is the portion of the milk which is produced 2 to 3 minutes after the flow begins. Hind milk is higher in fat and energy than foremilk but has similar concentrations of other nutrients as foremilk (*60*, *61*). Hind milk has been described as promoting greater weight gain than fore milk or regular breastmilk (*60*, *61*).

### Drip milk and expressed milk

The milk which drips from the opposite breast during breastfeeding is called drip milk and used to be provided in the 1980s for feeding pre-term infants. Drip breastmilk (DBM) differs from expressed breastmilk (EBM) both in its contents and in the change in its composition over the period of lactation. DBM is mainly fore milk; fat concentration and energy value are low, compared with levels reported for EBM. Protein, fat, sodium and energy values in DBM fall with the duration of lactation, whereas magnesium and calcium rise, and lactose, potassium, osmolality and lysozyme remain constant. The milk fat content of DBM produced by individual donors is linearly related to the daily volume of DBM produced (*62*, *63*). About 15% of lactating women produce drip milk; volumes produced are up to 188 ml/donor/day (*63*). Expressed breastmilk varies according to the type of technique used. Sodium levels have been shown to be higher after hand pumping than mechanical pumping, but this study did not control for breastmilk volume (*64*). Milk expressed by electric breast pumping also appears to have greater bacterial contamination than milk expressed by hand (*65–67*). WHO/UNICEF, the United Kingdom Association for Milk Banking, and the Human Milk Banking Association of North America have published guidelines for the expression and processing of breastmilk (*58*, *59*, *68*).

## Storage of human milk

### Heat treatment (pasteurization)

All donor milk should be pasteurized at 56–62 °C for 30 minutes to destroy micro-organisms including the human immunodeficiency (HIV) virus, human T-lymphotrophic virus type 1, and cytomegalovirus (CMV) which are excreted in breastmilk (*69–71*). Pasteurization also reduces the total bacterial content, provided the milk initially contained fewer than 106 bacteria/ml (*63*). However, pasteurization has also been shown to cause a significant reduction in IgA concentration and lysozyme activity, as well as a decrease in the ability of the milk to inhibit the growth of Gram-negative organisms. Pasteurization also reduces nitrogen retention, fat absorption (enzymes including milk lipase are destroyed), concentration of water-soluble vitamins, and antimicrobial factors such as viable leukocytes, immunoglobulins, lactoferrin, lysozyme, complement, specific antibodies to *Escherichia coli*, and folate-binding proteins (*72–75*).

Simpler methods (e.g. Pretoria pasteurization and flash treatment) to treat milk from HIV-positive women are emerging and have been reported to inactivate HIV (*76–79*). These methods can potentially be implemented in resource-poor areas. Pretoria pasteurization involves placing human milk in a container in a pan of boiling water for 20 minutes, then removing and cooling. Flash treatment involves placing human milk in a container, placing the container in a pan of room temperature water, then heating the water and milk together until it reaches a rolling boil (100 °C), and removing and cooling. Both methods are reported to decrease the concentrations of HIV although flash treatment may be more effective (see Section 7) (*76–79*).

### Refrigeration and freezing

Expressed human milk can be kept at room temperature for 6 hours before significant bacterial growth occurs (*80*, *81*). It has been suggested that human milk should be refrigerated at 3–4 °C to retard bacterial growth, maintain the stability of nutrients (except vitamin C), preserve the viability and function of leukocytes, and preserve the concentration of antimicrobial proteins (*82–84*). If mother's own milk needs to be refrigerated, it should not be for more than two days. Heat-treated breastmilk (mother's or donor) can be refrigerated for a maximum of 24 hours because of concerns that heating damages bacteriostatic mechanisms making the milk more susceptible to later contamination (*58*, *59*, *63*, *85*).

Human milk can also be frozen at –15 °C to –20 °C for up to 3 months. This will preserve most nutrients and antimicrobial proteins and maintain the stability of vitamins with antioxidant activity such as tocopherol and retinol (*86*, *87*). However, this process will significantly reduce the concentrations of vitamin C and milk leukocytes (*75*, *88*, *89*). IgA was found to be best preserved in frozen human milk by thawing either overnight in a refrigerator or by keeping under warm running water (*90*). Microwave thawing, particularly at temperatures above 60 °C, reduces the levels of IgA and lysozyme in breastmilk (*91*, *92*).

Freezing of breastmilk specimens naturally infected with cytomegalovirus (CMV) for 7 days or longer at –20 °C was believed to eliminate infectivity without destroying the biochemical and immunological qualities of the breastmilk (*93*). A more recent study that used more sensitive tests for quantitative detection of CMV in breastmilk has shown that late viral RNA and viral infectivity are preserved even after freezing at –20 °C for up to 10 days (*94*). Pasteurization removes CMV infectivity and should be carried out with donated milk. For a mother known to be infected with CMV, freeze storage of her own milk does not seem to be a perfect solution, but the rate of CMV transmission is likely to be lowered; the observed infections were asymptomatic (*95*).

## HUMAN MILK SUPPLEMENTS

Nutritional supplements, to be given separately from breastmilk, are available as single vitamin preparations (vitamin A, vitamin D, vitamin K) or single mineral preparations (iron, zinc, calcium and phosphorus). Multivitamin preparations are also available which contain vitamin A, vitamin D, thiamine, riboflavin, pyridoxine, nicotinamide, ascorbic acid (see Box 1.3.2). Multivitamins are not usually mixed into the breastmilk, but care is needed in administering the correct dose. Multivitamin preparations must be protected from light and refrigerated below 25 °C after opening.

Nutritional supplements are also available as additives to be mixed with human milk. Commonly known as 'fortifiers', they are commercially available and can be multicomponent (with added protein, carbohydrate, fat, calcium, phosphorus, sodium, vitamins A, D, E, K, riboflavin, folic acid and zinc) (see Box 1.3.3) or single component (protein, carbohydrate, fat, calcium, phosphorus or sodium).

Multicomponent fortifiers are available in powdered or liquid form. Powdered fortifiers may be insoluble in human milk, and unless the fortifier-milk mixture is well shaken, the nutrients may not be available for absorption. Liquid fortifiers are for use in a 1:1 ratio with human milk and contribute a significant pro-

**BOX 1.3.2 Nutrient composition of selected multivitamin supplement formulations**

| Multivitamins[a] | Pentavite 0.45 ml | Abidec 0.6 ml | Dalivit 0.6 ml |
|---|---|---|---|
| Vitamin A, IU | 4000 IU | 1333 IU | 5000 IU |
| Ergocalciferol Vitamin D, IU | 400 IU | 400 IU | 400 IU |
| Vitamin C, mg | 43 mg | 40 mg | 50 mg |
| Vitamin $B_1$, mg | 0.54 mg | 0.4 mg | 1 mg |
| Vitamin $B_2$, mg | 0.81 mg | 0.8mg | 0.4 mg |
| Pantothenic acid, mg | 0.288 mg | — | — |
| Vitamin $B_6$, mg/g protein | 0.14 mg | 0.8 mg | 0.5 mg |
| Niacin, mg | 7.11 mg | 8 mg | 5 mg |

[a] Usually provided as 0.45ml Pentavite or 0.6 ml Abidec/Dalvit once daily orally after a feed (not per kg)

**BOX 1.3.3 Nutrient composition of commercial multicomponent human milk fortifiers**

| | Powdered multicomponent human milk fortifiers | | | | | | |
|---|---|---|---|---|---|---|---|
| Nutrient | Enfamil human milk fortifier | Similac human milk fortifier | SMA breastmilk fortifier | Milupa Eoprotin | Nutriprem Cow & Gate | Aptamil FMS Milupa | $FM_{85}$ Nestle |
| Quantity | 4 g | 4 g | 4 g | 3 g | 3 g | 3.4 g | 5 g |
| **Macronutrients** | | | | | | | |
| Energy, kcal | 14 | 14 | 15 | 11 | 10 | 12 | 18 |
| Protein, g | 1.1 | 1 | 1 | 0.6 | 0.7 | 0.8 | 0.8 |
| Fat, g | 0.65 | 0.36 | 0.16 | 0.02 | 0 | 0 | 0.015 |
| Carbohydrate, g | 1.1 | 1.8 | 2.4 | 2.1 | 2 | 2.2 | 3.6 |
| **Minerals** | | | | | | | |
| Calcium, mg | 90 | 117 | 90 | 38 | 60 | 69 | 51 |
| Phosphorus, mg | 45 | 67 | 45 | 26 | 40 | 46 | 34 |
| Magnesium, mg | 1 | 7 | 3 | 2.1 | 6 | 6.8 | 2 |
| Sodium, mmol | 0.5 | 0.7 | 0.8 | 0.9 | 0.3 | 0.3 | 1.2 |
| Chloride, mmol | 0.3 | 1.1 | 0.5 | 0.4 | 0.2 | 0.2 | 0.5 |
| Potassium, mmol | 0.5 | 1.6 | 0.7 | 0.006 | 0.1 | 0.1 | 0.3 |
| Iron, mg | 1.44 | 0.35 | 0 | 0 | 0 | 0 | 0 |
| Zinc, mcg | 720 | 1000 | 260 | 0 | 300 | 350 | 0 |
| Copper, mcg | 44 | 170 | 0 | 0 | 26 | 30 | 0 |
| Manganese, mcg | 10 | 7.2 | 4.6 | 0 | 6 | 10 | 0 |
| **Vitamins** | | | | | | | |
| Vitamin A, mcg | 285 | 186 | 270 | 30 | 130 | 150 | 0 |
| Vitamin E, mg | 4.6 | 3.2 | 3 | 0.3 | 2.6 | 2.9 | 0 |
| Vitamin $K_1$, mcg | 4.4 | 8.3 | 11 | 0.2 | 6.3 | 7.1 | 0 |
| Vitamin D, mcg | 4 | 3 | 7.6 | 0 | 5 | 5.7 | 0 |
| Vitamin C, mg | 12 | 25 | 40 | 15 | 12 | 14 | 0 |
| Thiamine, mcg | 150 | 233 | 220 | 0 | 130 | 150 | 0 |
| Riboflavin, mcg | 220 | 417 | 260 | 0 | 170 | 190 | 0 |
| Vitamin $B_6$, mcg | 115 | 211 | 260 | 0 | 110 | 120 | 0 |
| Vitamin $B_{12}$, mcg | 0.18 | 0.64 | 0.3 | 0 | 0.2 | 0.2 | 0 |
| Niacin, mg | 3 | 3.57 | 3.6 | 0 | 2.5 | 2.8 | 0 |
| Folic acid, mcg | 25 | 23 | 0 | 0 | 50 | 57 | 0 |
| Biotin, mcg | 2.7 | 26 | 0 | 0 | 2.5 | 2.8 | 0 |
| Pantothenic acid, mg | 0.73 | 1.5 | 0 | 0 | 0.75 | 0.85 | 0 |
| Increment in osmolality, mOsm | 63 | 90 | 137 | 70 | 60 | 57 | 105 |

From: Reference number *46*

portion of the infant's fluid intake. Although they are designed to contain adequate quantities of all essential nutrients, mixing the mother's own milk with an equal volume of liquid fortifier dilutes the constituents of the human milk, including nutrients, growth factors and anti-infective properties (*96*).

## BREASTMILK SUBSTITUTES

Breastmilk substitutes are available in many different formulations and their nutrient composition varies markedly. They do not contain biologically active anti-infective or immune substances, or the hormones and growth factors that are found in human milk. All breastmilk substitutes have a risk of contamination, particularly if prepared and handled incorrectly.

### Types of available breastmilk substitutes

#### Locally prepared animal milks

Raw animal milk is often contaminated with pathogenic organisms (such as *Brucella melitensis*) and is an excellent culture medium. Raw animal milk should be pasteurized by heating to 56–62 °C for 30 minutes before any other modifications and definitely before administration (*97*).

It is also important to note that the concentrations of nutrients in cow, goat and buffalo milk are suboptimal when compared to human milk. Animal milk has low concentrations of iron, folic acid, vitamin D, vitamin $B_{12}$, vitamin C, vitamin E and long-chain polyunsaturated fatty acids. The bioavailability of the small quantity of iron present in animal milk is also low. Animal milk has high protein, electrolyte, mineral and fat content compared to human milk and must be diluted (2 parts of milk to 1 part of water). Dilution diminishes the energy and micronutrient content which can be partially compensated by adding sugar (10 g/100ml undiluted milk). Additional vitamins, minerals and fat/oils are also needed, but these are rarely added and result in an expensive preparation (*98–100*). Multivitamin complex has been proposed, but feasibility is limited due to the small doses needed in LBW newborns.

#### Standard infant formulas

Standard infant formulas are designed for term infants and are based on the composition of mature breastmilk. The typical energy content is 68 kcal/100ml. Protein concentration is approximately 1.5 g/100ml, and calcium and phosphorus are 50 mg/100ml and 30 mg/100ml respectively. Product information from the manufacturers can be found in Box 1.3.4.

#### Pre-term infant formulas

Pre-term infant formulas are designed for pre-term infants. These are calorie-enriched (approximately 80 kcal/100ml) and variably protein- and mineral-enriched to support intra-uterine nutrient accretion rates. Calories may be provided as protein, fat or carbohydrate and the balance between calories and protein may be critical in determining the type of growth. Product information from the manufacturers can be found in Box 1.3.4.

Compared to unsupplemented human milk, pre-term formula contains more protein, sodium, calcium, phosphorus, zinc, copper and vitamins, often in a form that is easily absorbed and metabolised. Most have an energy content of about 80 kcal/100ml. In spite of the higher carbohydrate and mineral content, the osmolality of pre-term formulas remains low at around 250–320 mOsm/kg $H_2O$. Pre-term formulas contain at least 2 g/100ml of protein so that the pre-term infant will receive 3 g/kg/d of protein when fed 150 ml/kg/d.

#### Nutrient enriched "post-discharge" formulas

These formulas are used in some developed countries for feeding pre-term babies after discharge from hospital for a few weeks before they are started on term infant formula. Post-discharge formulas are intermediate in composition between pre-term and term infant formulas. Product information from the manufacturers can be found in Box 1.3.5. Compared to unsupplemented human milk, post-discharge formulas contain more protein, sodium, calcium, phosphorus, zinc, copper and vitamins. Most have an energy

**BOX 1.3.4 Nutrient composition of standard and pre-term infant formulas**

| Formulation | Concentration of constituents (units/L) | | |
|---|---|---|---|
| | Standard infant formula | Pre-term infant formula | |
| | | Osterprem FHP | Enfamil premature |
| **Macronutrients** | | | |
| Energy, kJ/L (kcal/L) | 2,840 (680) | 3,360 (800) | 2856 (680) |
| Protein, g/L | 14.5 | 20 | 20.4 |
| Fat, g/L | 38.2 | 46 | 34.7 |
| Carbohydrate, g/L | 69.6 | 76.5 | 74.8 |
| **Minerals** | | | |
| Calcium, mg/L | 390 | 1100 | 1122 |
| Phosphorus, mg/L | 270 | 630 | 564 |
| Magnesium, mg/L | | 50 | 61.2 |
| Sodium, mg/L | 170 | 420 | 394 |
| Chloride, mg/L | 450 | 600 | 612 |
| Potassium, mg/L | 570 | 720 | 666 |
| Iron, mg/L | 6.5 | 0.400 | 12.2 |
| Zinc, mg/L | 3.4 | 8.800 | 10.2 |
| Copper, µg/L | 420 | 960 | 816 |
| Manganese, ug/L | 34 | 30 | 42.8 |
| Iodine, µg/L | 45 | 80 | 170 |
| **Vitamins** | | | |
| Vitamin A, ug/L | 1000 | 1000 | 2550 |
| Vitamin E, mg/L | 48 | 100 | 19.3 |
| Vitamin K, µg/L | 27 | 70 | 54.4 |
| Vitamin D, µg/L | 10 | 24 | 408 |
| Vitamin C, mg/L | 69 | 280 | 136 |
| Vitamin $B_1$, ug/L | 420 | 950 | 1360 |
| Vitamin $B_2$, µg/L | — | 1800 | 2040 |
| Vitamin $B_6$, µg/L | 350 | 1000 | 1020 |
| Vitamin $B_{12}$, µg/L | 1.4 | 2 | 1.7 |
| Niacin, µg/L | — | 10,000 | 27200 |
| Folate, µg/L | 34 | 500 | 272 |
| Biotin, µg/L | 10 | 20 | 27.2 |
| Osmolality, mOsmol/L | 300 | 250–320 | 250–320 |

content of about 80 kcal/100 ml (24 kcal/oz), osmolality at around 250–320 mOsm/kg $H_2O$, and at least 2 g/100 ml of protein.

## Soy-based formulas

Soy protein in these formulas is felt to be of low bioavailability for LBW infants. Other problems reported include low plasma levels of methionine, chloride and iodine, and a high content of aluminium and phytoestrogen. Clinical problems in LBW infants have included hypochloraemic metabolic alkalosis and growth impairment (*101*).

## High-protein formulas

Raising the protein intake from 2 to 4 g/kg/d in LBW infants has been shown to increase weight gain, linear growth, nitrogen retention and serum albumin (*102*). Increasing the protein intake further from 4 to 6 g/kg/d does not result in more weight gain but is associated with fever and lethargy and, on follow-up, an increased incidence of strabismus and low developmental scores (*103*, *104*).

**BOX 1.3.5 Nutrient composition of nutrient enriched 'post-discharge' formulas**

| | Concentration of constituents (units/L) | | |
|---|---|---|---|
| | Term | Nutrient enriched 'post discharge' | |
| | Standard | Farley's premcare | Nutriprem 2 |
| **Macronutrients** | | | |
| Energy, kJ/L (kcal/L) | 2,840 (680) | 3,010 (720) | 3,000 (700) |
| Protein, g/L | 14.5 | 18.5 | 18 |
| Fat, g/L | 38.2 | 39.6 | 38 |
| Carbohydrate, g/L | 69.6 | 72.4 | 70 |
| **Minerals** | | | |
| Calcium, mg/L | 390 | 700 | 710 |
| Phosphorus, mg/L | 270 | 350 | 350 |
| Sodium, mg/L | 170 | 220 | 250 |
| Chloride, mg/L | 450 | 450 | 460 |
| Potassium, mg/L | 570 | 780 | 800 |
| Iron, mg/L | 6.5 | 6.5 | 6.5 |
| Zinc, mg/L | 3.4 | 6.0 | 6.0 |
| Copper, µg/L | 420 | 570 | 600 |
| Manganese, ug/L | 34 | 50 | 45 |
| Iodine, µg/L | 45 | 45 | 45 |
| **Vitamins** | | | |
| Vitamin A, µg/L | 1000 | 1000 | 1000 |
| Vitamin E, mg/L | 4.8 | 15 | 15 |
| Vitamin K, µg/L | 27 | 60 | 60 |
| Vitamin D, µg/L | 10 | 13 | 12 |
| Vitamin C, mg/L | 69 | 150 | 160 |
| Vitamin $B_1$, µg/L | 420 | 950 | 900 |
| Vitamin $B_2$, µg/L | 550 | 1000 | 1000 |
| Vitamin $B_6$, µg/L | 350 | 800 | 800 |
| Vitamin $B_{12}$, µg/L | 1.4 | 2.0 | 2.0 |
| Folate, µg/L | 34 | 250 | 250 |
| Biotin, µg/L | 10 | 11 | 12 |
| Panthothenic acid, mg/L | 2.3 | 4.0 | 4.2 |
| Osmolality, mOsmol/L | 300 | 280 | 280 |

## Medium-chain triglyceride-enriched formulas

High medium-chain triglyceride content in pre-term infant formula has been associated with a higher incidence of adverse gastrointestinal effects including abdominal distension, increased gastric aspirates, vomiting, loose stools and necrotising enterocolitis (*105*). In addition, medium-chain triglyceride-enriched formulas have not been shown to improve fat absorption, energy storage, nitrogen retention or growth (*105*).

## Powdered and liquid infant formulas (standard or pre-term)

Commercial liquid infant formulas are produced by a sterile process which is expensive. Powdered infant formulas are not prepared by a sterile process and, as a consequence, are not sterile. Some unopened cans may be contaminated with *Enterobacter sakazakii* and *Salmonella*. Keeping the reconstituted liquid formula at room temperature for longer than 4 hours is thought to multiply the amount of bacteria already present. There have also been recent US reports of outbreaks of nosocomial infections in pre-term neonates administered milk-

based powdered infant formulas (*106–108*). Recently, a batch of Portagen infant formula was found to be contaminated by *Enterobacter sakazakii*. Administration of Portagen formula led to the death of one infant (*106*). This is the first report of *E. sakazakii* infection associated with infant formula, prompting recall of a commercial product in the US. Significantly, the results of another investigation (the "Belgium outbreak") suggest that even low levels of *E. sakazakii* in milk-based powdered infant formula (i.e. within the 1994 Codex Alimentarius limits for the presence of coliforms in milk-based powdered infant formula) can lead to development of infection (*107*).

An expert meeting convened by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) on *E. sakazakii* and other microorganisms in powdered infant formula (*109*) concluded that intrinsic contamination of powdered infant formula with *E. sakazakii* and *Salmonella* has been a cause of infection and illness in infants, including severe disease which can lead to serious developmental sequelae and death. No link has been established between illness and other microorganisms in powdered infant formula, although such a link was considered plausible for other Enterobacteriaceae. Infants at greatest risk for *E. sakazakii* infection are neonates (first 28 days), particularly pre-term infants, LBW infants or immunocompromised infants. The meeting did not identify a feasible method, using current technology, to produce commercially sterile powders or completely eliminate the potential of contamination. Even low levels of contamination of *E. sakazakii* in powdered infant formula were considered to be a risk factor, given the potential for multiplication during preparation and the time between preparation and consumption of reconstituted formula. Based on a preliminary risk assessment, the inclusion of a step lethal for the bacteria at the point of preparation of the feed and decreasing the time between preparation and consumption effectively reduced the risk. A combination of intervention measures had the greatest impact. Recommendations included, among others, that in situations where infants are not breastfed, carers of high-risk infants should be encouraged to use, whenever possible and feasible, commercially sterile liquid formula or formula which has undergone an effective decontamination procedure (e.g. using boiling water to reconstitute and heating the reconstituted formula) at the point of use (*109*).

## 1.4 Development of feeding ability

### NEUROMUSCULAR SYSTEM

Term SGA infants have been described as having the same developmental characteristics as their AGA counterparts (*110*, *111*). In contrast, distinct central and peripheral neurodevelopmental milestones have been described in pre-term infants. Taste develops at 12–15 weeks gestation, smell at about 20 weeks, and hearing begins at approximately 20–24 weeks. Prior to 28 weeks of gestation it is difficult to identify periods of wakefulness. Persistent stimuli lead to eye opening and closing for time periods measured principally in seconds (*112*, *113*). At approximately 28 weeks gestation, however, there is a distinct change in the level of alertness (*112*, *114*). At that time a gentle shake will arouse the infant from apparent sleep and will result in wakefulness for several minutes. Spontaneous alerting also occasionally occurs at this age. By 32 weeks, stimulation is no longer necessary. The eyes are often open and spontaneous roving eye movements appear (*112*, *113*). By 36 weeks increased alertness can be observed readily and vigorous crying appears during wakefulness. By term, the infant exhibits distinct periods of attention to visual and auditory stimuli (*112*, *113*, *115*).

The early components of sucking appear to occur in fetuses at about 7–8 weeks gestational age (*110*, *116*, *117*). At 8 weeks gestation the fetus will respond to touch around the mouth area. Swallowing is present at around 11–16 weeks and sucking appears at 18–24 weeks (*116–118*). The gag reflex is evident at 25–27 weeks although organized oesophageal activity does not develop until about 32 weeks ges-

tation and is not coordinated with swallowing until about 33–34 weeks. By 33–34 weeks gestation, pre-term infants are also mature enough to coordinate a swallow and breathe pattern. The normal infant is then able to maintain a concerted synchronous action for productive oral feeding (*116–118*).

By 32–34 weeks the infant should be able to attach, suck and extend the tongue appropriately and begin breastfeeding. As long as the baby is able to keep the breast tissue in the mouth the infant's peristaltic tongue movement can remove milk from the lactiferous sinuses within the area of the areola (*116*, *118*, *119*). The rooting reflex (the response shown by a baby after the side of the cheek is touched – the infant turning to the breast with the mouth wide open) occurs around this time. Maturation continues and coordinated and effective use of the suck, swallow and breathing reflexes for nutritive purposes is achieved fully by 35–37 weeks gestation (*116*, *120*).

The infant is developmentally ready for complementary feeding from 4 months of corrected age. Phasic biting disappears between 3 and 4 months and rooting diminishes between 5 and 6 months. Stability of the trunk also improves at this time and the infant begins to be able to sit unsupported. Finger coordination develops by 6–7 months of age to permit finger-feeding. By 12 months of age, rotary chewing is well established with controlled, sustained biting, and most infants are capable of spoon-feeding themselves (*110*, *121*).

## ENDOCRINE AND EXOCRINE SYSTEMS

Rate-limiting enzymes for gluconeogenesis develop late in gestation (*122*). Gluconeogenesis is triggered hormonally after birth, but this process is ineffective at meeting the glucose needs for cerebral metabolism (*123*). Achieving glucose homeostasis in the newborn infant is dependent on exogenous sources. Enteral feeding induces the gut endocrine response, which mediates many metabolic and gastrointestinal adaptive changes (*124*, *125*). Basal and postprandial plasma concentrations of several hormones (especially enteroglucagon, gastrin and insulin) increase according to the quality and type of feed (*126*). These surges are even more marked in pre-term than term infants and occur even when nutritionally insignificant volumes of less than 1 ml/kg/day are fed. Absorptive capacity is also thought to increase rapidly on feeding (*126*, *127*). Premature babies, particularly those with birth weights <1100 g, are at risk of glucose intolerance (*128*). Two proposed mechanisms include inappropriate secretion of insulin by the pancreas and decreased sensitivity of the liver to the gluco-regulatory effect of insulin (*129*). Alpha-glucosidases and lactase are both required to digest lactose. The activity of alpha-glucosidases in the fetus reaches at least 70% of the activity in adults at a gestational age of about 26–34 weeks, whereas lactase activity at that gestational age is only 30% of adult activity (*130*, *131*). Although theoretically lactose digestion should be limited, there is no evidence of clinical intolerance among LBW infants. Pancreatic lipase secretion and bile salt concentrations are also low in comparison with the levels at term, but lingual and gastric lipases are detectable in the fetus from 26 weeks gestation and can assist in gastric lipolysis (*131*, *132*).

## GASTROINTESTINAL SYSTEM

The gastrointestinal tract is anatomically complete at 24 weeks gestation but is functionally immature in both propulsive and absorptive capacity. Gastric emptying is slower in preterm than term infants and fasting antral pressure is significantly reduced (*133*, *134*). Fetal small bowel transit appears at 28 weeks gestation but peristalsis is poorly organized. Motor activity in the gastrointestinal tract is random up to about 30 weeks gestational age. Over the next 5–6 weeks it becomes clustered phasic and then prolonged phasic. Migrating motor complexes appear near term (*135*). Combined with high lower oesophageal sphincter pressures, this immaturity may predispose the immature infant to gastro-oesophageal reflux and result in feeding intolerance (*136–139*). Large enteral intakes may also not be tolerated. Gastric capacity is also limited in LBW infants and gastric distension may interfere with pul-

monary function (*133*, *140*). Little is known about the morphological aspects of adaptation in the immature human gut, but animals show both hyperplasia and hypertrophy in response to feeding and the milk of the young's own species may be especially effective (*141*).

# 2. NUTRITION

## 2.1 Human milk

Human milk is the recommended nutritional source for full-term AGA infants – exclusively for the first 6 months of postnatal life and in combination with complementary foods until the infant reaches 2 years of age (*142–144*). Extensive research, especially in recent years, documents many advantages to infants, mothers, families, and society from breastfeeding and from use of human milk for infant feeding (*142–145*).

The role of human milk for LBW infants is reviewed here. Human milk may be provided directly via breastfeeding, or as expressed mother's own milk, or as expressed donor-pooled pre-term or term milk. Different clinical outcomes are likely depending on whether the mother's own or donor human milk is used and whether it has been pasteurized, frozen or refrigerated. Impacts may also differ depending on whether the infants are fed human milk soon after delivery or in later infancy. The question of optimal duration of exclusive breastfeeding for LBW infants also needs to be addressed.

The following issues are reviewed below:

(1) Breastfeeding and mother's own expressed milk
(2) Donor human milk
(3) Optimal duration of exclusive breastfeeding.

### (1) BREASTFEEDING AND MOTHER'S OWN EXPRESSED MILK

#### Results

#### Effects on mortality

No studies were located which examined the impact of mother's own milk on mortality rates in LBW infants.

#### Effects on severe morbidity – infection

Five studies on the effect of feeding mother's own milk, compared with formula feeding, on the risk of infection were located (level of evidence LIII-2 or higher) and have been summarized in Table 2.1.1 (*146–150*). Two of these are RCTs conducted in India in the 1980s and compared unsupplemented mother's milk with term infant formula (*146*, *147*). A UK cohort study compared unsupplemented mother's milk with pre-term infant formula (*148*), and two US studies compared mother's own milk supplemented with multicomponent human milk fortifier or pre-term infant formula (*149*, *150*). These studies included LBW infants of varying gestational age and birth weight. One of the cohort studies from the US did not adjust for confounding (*150*). There is a striking consistency in the results despite differences in study design, settings, participants and comparison groups (see summary table 2.1.1). Feeding mother's milk was found to be protective against infection (systemic or local infection, and necrotising enterocolitis) in all the studies.

#### Effects on neurodevelopment

A number of early studies were located which examined the impact of unsupplemented mother's own milk to formula milk on neurodevelopmental outcomes in LBW infants (*151–155*). Most of these studies were conducted in pre-term infants. The largest of them was a cohort study conducted by Lucas et al in the UK (n=771) (*154*, *155*). Lucas et al followed infants to 8 years of age and demonstrated an 8-point advantage in intelligence quotient even after controlling for mother's education and social class. Variable results were reported from the other smaller cohort studies. A meta-analysis of all available studies to 1996 indicated that after adjust-

ment for appropriate key cofactors, unsupplemented breastfeeding, compared to formula milk feeding, was associated with significantly higher intelligence quotient scores (5.18 points higher; 95%CI: 3.59, 6.77) in LBW infants (*156*) (see summary table 2.1.2).

Four studies published after the meta-analysis are also noteworthy. A recent large multicentre trial from Chile, the UK, and the US (n = 463 preterm infants <33 weeks gestational age) did not find a significant difference in IQ scores between the group predominantly fed supplemented human milk and the group predominantly fed formula until term chronological age (*157*). However, there was a positive association between the duration of feeding with supplemented mother's own milk and the Bayley Mental Index at 12 months chronological age (P=0.032), after adjusting for confounding variables of home environment and maternal intelligence. In a study conducted in term SGA infants, the duration of EBF had a significant impact on cognitive development without compromising growth (*153*). Another study, which assessed 137 infants born SGA at 12 months of age, found that breastfed infants had higher motor development scores whereas there was no difference in other aspects of development (*158*). A recent study reported substantial benefits of breastfeeding for neurodevelopment in children born SGA. Infants of mothers who chose to breastfeed had significantly higher scores for mental development (adjusted mean difference (MD) 8.2, 95%CI 5.0, 11.4) and psychomotor development (adjusted MD 5.8, 95%CI 2.8, 8.7) at 24 months of age, compared with infants whose mothers chose to formula feed (*159*) (see summary table 2.1.2).

### Effects on malnutrition

A number of studies were located which reported slower growth, in both weight and length, in pre-term infants <32 weeks gestation who were fed unsupplemented breastmilk before hospital discharge, compared to those who were formula fed (*150*, *157*). However, only one study reporting the impacts of mother's own milk on anthropometric standard deviation scores and malnutrition was located. Lucas et al examined the impacts of breastfeeding, compared to formula milk, in post-discharge pre-term infants (*160*). In this study all breastfed infants had lower standard deviation scores than formula-fed infants at 9 months. However, only the difference in length was statistically significant and no score was below –2 standard deviation scores.

In term SGA infants, a recent UK cohort study (n=474) reported no significant differences in mean weight, length and head circumference in breastfed compared to formula-fed infants at 18 months of chronological age (*161*).

### Effects on other important outcomes

Specific nutrient deficiencies in infants fed unsupplemented mother's own milk from birth have also been described in many case series from the 1960s and 1970s. Iwai et al and James and Combes reported that 80–90% of infants who weighed less than 2500 g at birth, fed unsupplemented human milk, developed *iron deficiency anaemia* (haemoglobin concentration <11 g/dl) by 6 months of age (*162*, *163*). Widdershoven et al reported high rates of clinical *vitamin K deficiency* (haemorrhagic disease of the newborn) in term and pre-term infants of less than 36 weeks gestation, who were fed unsupplemented mother's own milk (*164*). Before the 1990s, a high percentage of infants, especially those of birth weight <1500 g, fed unsupplemented maternal milk were reported with *osteopaenia, fractures* and *rickets* before hospital discharge (*165–168*). Other case series have indicated that *deficiencies of zinc, vitamin A* and *vitamin D* may develop in the exclusively breastfed LBW infant (*169–173*). Infants who weigh less than 1500 g at birth are especially at risk.

## Conclusions and implications

Most of the findings of this section are based on observational studies, mainly from developed countries. It is important to note that even the strong effect in these observational studies may not imply causality because of the possibility of selection and measurement biases,

and confounding by factors that were not included in the multivariate analyses. Overall, the above findings illustrate the importance of providing mother's own breastmilk to all LBW infants.

### Infants <32 weeks gestation (or birth weights <1500 g if gestation is not available)

In this group of LBW infants, there is strong and consistent evidence that feeding mother's own milk is associated with a lower incidence of infection, including necrotising enterocolitis. There is also clear evidence that this feeding modality is associated with improved neurodevelopmental outcome. Feeding unsupplemented mother's own milk has been shown to result in slower ponderal and linear growth, but the implications of this slower growth are unclear and there is not enough evidence to assess if it increased the risk of malnutrition. Also, feeding unsupplemented mother's own milk may result in deficiencies of some micronutrients. Breastmilk feeding should be preferred over formula feeding because of clear benefits related to infection and neurodevelopment. Supplementation of breastmilk with macronutrients and micronutrients is required for this group of LBW infants.

### Infants 32–36 weeks gestation (or birth weights 1500–2000 g if gestation is not available)

The conclusions for this group of LBW infants are similar to those for infants <32 weeks gestation with regard to infection and neurodevelopment. There is no clear evidence of adverse effects of feeding mother's own milk on growth. However, feeding only mother's own milk may result in deficiencies of some micronutrients. Breastmilk feeding should be preferred over formula feeding because of clear benefits related to infection and neurodevelopment. Supplementation with some micronutrients is required for this group of LBW infants.

### Term LBW infants (or birth weights >2000 g if gestation is not available)

There is paucity of data on most outcomes in this subgroup of LBW infants. The available data suggest that the benefits of feeding mother's milk, as related to infection and neurodevelopment, are similar to that of pre-term infants. There seems to be no adverse effect of this modality of feeding on growth. Breastmilk feeding should therefore be preferred over formula feeding because of benefits related to infection and neurodevelopment. Supplementation with some micronutrients may be required for this group of LBW infants.

Although most of the studies included in this section were from developed countries, the few available studies from developing country settings showed similar results. Breastfeeding and feeding mother's expressed breastmilk is likely to have an even greater impact on infections in developing countries than the impact seen in the reviewed studies because of higher incidence of infections in these settings. There are no reasons to believe that the benefits of breastfeeding or feeding mother's expressed breastmilk on neurodevelopment would be lower in developing countries than those found in this review.

## Recommendations

Policy statements from WHO, UNICEF and other international and national organizations confirm the importance of providing mother's own milk to pre-term and SGA infants. Standard practice in neonatal units is to promote mother's own milk as the feed of choice for all LBW infants. The findings of this review support this recommendation.

**SUMMARY TABLE 2.1.1**
**Effects of mother's own milk compared with formula feeding on infection or necrotising enterocolitis in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Narayanan et al (*146*) RCT (LII) | Birth weight <2500 g, at high risk of infection | 10% | 57% | 33% | Unsupplemented expressed breastmilk during day and standard infant formula during night (n=32) *compared with* standard infant formula only (n=38) | Systemic or local infection from birth to hospital discharge | RR 0.44 [0.24, 0.82] |
| Narayanan et al (*147*) RCT (LII) | Birth weight <2500 g, at high risk of infection | 8% | 64% | 24% | 10 ml colostrum 3 times a day until 72 hours of age along with standard infant formula (n=33) *compared with* standard infant formula only (n=33) | Systemic or local infection from birth to hospital discharge | RR 0.39 [0.19, 0.81] |
| Lucas & Cole (*148*) Cohort (LIII-2) | Birth weight <1850 g | 66% | 34% | None | Unsupplemented expressed breast milk only (n=253) *compared with* standard or pre-term formula only hospital (n=236) | Necrotising enterocolitis from birth to discharge | Adjusted[b] OR 0.09 [0.03 to 0.33] |
| | | | | | Formula plus breastmilk (n=437) *compared with* standard or pre-term formula only (n=236) | Necrotising enterocolitis from birth to hospital discharge | Adjusted[b] OR 0.29 [0.12 to 0.67] |
| Hylander et al (*149*) Cohort (LIII-2) | Pre-term infants with birth weight <1500g | 95% | 5% | None | Fortified expressed breast milk along with pre-term formula (n=123) *compared with* pre-term formula only (n=89) | Systemic or local infection from start of enteral feeding to hospital discharge | Adjusted[c] OR 0.43 [0.23 to 0.81] |
| Schanler et al (*150*) Cohort (LIII-2) | 26–30 wk gestation, postnatal age ≤96 hours | 100% | None | None | Predominantly fed fortified expressed breastmilk (n=62) *compared with* pre-term formula only (n=46) | Late onset sepsis or necrotising enterocolitis | RR 0.56 [0.36 to 0.89] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those with 1501–2000 g to be 32–36 wk gestation, and those with 2001–2500 g to have a gestation of 37 weeks or more.

[b] Adjusted for length of gestation, birth weight, sex, birth asphyxia, previous blood transfusions, use of theophylline and frusemide, polycythaemia, respiratory disease, duration of umbilical artery catheterization, age at first enteral feed, rate of progression of early feed volumes, and maternal steroid treatment.

[c] Adjusted for gestational age, 5-minute APGAR score, mechanical ventilation and days without enteral feedings.

**SUMMARY TABLE 2.1.2**
**Effects of mother's own milk compared with formula feeding on neurodevelopment in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Outcome measure | Comparison groups | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Anderson et al (*156*) Meta-analysis of cohort studies (LIII-2) | 3 studies, one each with: birth weight <1850 g, 500–1500 g and <2537 g | 25% | 50% | 25% | Breastfed (n=1254) *compared with* formula-fed (n=751) | Cognitive development scores | Adjusted [b] difference in mean scores 5.18 [3.59, 6.77] |
| Rao et al (*153*) Cohort (LIII-2) | Term SGA infants | 0 | 0 | 100% | Exclusively breastfed for >12 wk (n=81) *compared with* exclusively breastfed for ≤12 wk (n=139) | Total IQ score on Wechler Preschool and Primary Scales of Intelligence | Adjusted[c] difference in mean scores 5.0 [0.7 to 9.3] |
| Morley et al (*159*) Cohort (LIII-2) | Term SGA infants | 0 | 0 | 100% | Mother chose to breastfeed (n=137) *compared with* mother chose to formula feed (n=235) | Bayley mental development score at 18 months age | Adjusted[d] difference in mean scores 8.2 [5.0 to 11.4] |
| | | | | | | Bayley psychomotor development score at 18 months age | Adjusted[d] difference in mean scores 5.8 [2.8 to 8.7] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.
[b] Results included from studies that adjusted for at least 5 of the following variables: duration of breastfeeding, sex, maternal smoking history, maternal age, maternal intelligence, maternal education, maternal training, paternal education, race or ethnicity, socioeconomic status, family size, birth order, birth weight, gestational age, and childhood experiences.
[c] Adjusted for site of enrolment, maternal education, maternal IQ, maternal smoking, admission to a neonatal care unit, kindergarten attendance, gender and asymmetric intrauterine growth retardation.
[d] Adjusted for child's gender and birth order, maternal age, education score, social class, maternal head circumference, and height and whether mother smoked during pregnancy.

## (2) DONOR HUMAN MILK

### Results

The feeding options for LBW infants, particularly when breastfeeding is not possible, include donor milk and artificial infant formula. To make appropriate choices, it is important to consider the relative advantages and disadvantages of these milks. The results of studies comparing the effect of donor human milk with that of artificial infant formula on important outcomes are summarized below.

#### Effects on mortality

No studies were located which compared the impact of donor human milk to formula milk on mortality rates in LBW infants.

#### Effects on severe morbidity – infection

A meta-analysis was located of all available RCTs till the year 2003, which examined the impacts of donor human milk and formula milk on rates of necrotising enterocolitis in pre-term infants <1850 g (Level I evidence) (*148*, *174–177*). All four trials, conducted in developed countries in the 1980s and early 1990s, compared infants who were fed unsupplemented drip donor milk with those fed standard or calorie-enriched formula; the milk feed comprised the infant's sole diet for at least 1 month during the initial phases of hospital admission.

None of the individual trials found any statistically significant results, but the point estimates in 3 of the 4 trials were in the direc-

tion of a lower risk of necrotising enterocolitis in the donor milk group (*148*, *175*, *176*). However, the meta-analysis demonstrated a borderline statistically significant difference in the incidence of possible or confirmed necrotising enterocolitis (*174*). A more recent RCT in VLBW infants also reported no difference between infants provided with pre-term formula and those receiving supplemented expressed donor milk on rates of serious infection and necrotising enterocolitis (*178*) (see summary Table 2.1.3).

### Effects on neurodevelopment

Two RCTs were located which examined the impacts of donor human milk, compared to pre-term formula, on neurodevelopmental outcomes; these are summarized in Table 2.1.4 (Level II evidence) (*16*, *177*). In both trials, infants were randomized to receive unsupplemented drip donor term milk or calorie-enriched pre-term formula from birth until hospital discharge. Tyson et al measured Brazelton Neonatal Behavioural Assessment Scales at 37 weeks gestational age and reported that the group of infants who received standard infant formula milk had greater mean scores than the infants who received donor milk (*177*). However, Lucas et al examined neurodevelopmental outcomes at 18 months chronological age and did not find any statistically significant differences in developmental quotients in the group of infants allocated to receive standard infant formula compared with donor term human milk, though the confidence intervals of the effect sizes were large (see summary Table 2.1.4) (*16*).

In a non-random comparison across two RCTs, Lucas et al reported that infants fed donor milk had significantly higher motor development scores at 18 months but no significant difference in mental development scores (see summary Table 2.1.4).

### Effects on malnutrition

A number of RCTs which randomized infants ≤1850 g to receive unsupplemented term donor milk before hospital discharge or infant formula (Level II evidence) were located (*176*, *178–182*). All trials reported that feeding with formula milk was associated with a statistically significant increase in at least one growth parameter (mean gain in weight, length or head circumference) by the time of hospital discharge, compared with unsupplemented donor drip milk. Expressed supplemented donor milk also had significantly lower growth rates compared with both term and pre-term infant formula. However, no longer-term impacts on growth parameters were reported in the one trial that followed infants to 7½–8 years (*182*). No studies were located which examined the impacts on standard deviation scores or rates of malnutrition.

### Effects on other important outcomes

Singhal et al recently reported on *adult onset chronic disease* outcomes in a subsample of the original cohort of pre-term infants with birth weights <1850 g (n=130) (Level II evidence) (*24*, *25*, *183*). Blood pressure measurements were significantly lower in 16-year-old males who had received donor milk in their first month of life than those given standard infant formula. In addition, fasting proinsulin concentrations indicative of a prodromal phase of diabetes mellitus were higher in the children given standard infant formula than in those given donor human milk (mean difference 20·6% [95%CI 5·0 to 36·3]). Lucas and Morley did not, however, find a difference in blood pressure in the study groups at an earlier age (8–9 years) in the same cohort (*184*). No other studies were located in LBW infants which examined these factors.

Only Lucas et al examined the impacts of donor compared to formula milk on *bone mineralization* in pre-term infants who weighed <1850 g at birth (Level II evidence) (*185*, *186*). At 8–12 years, no significant differences in anthropometry, bone mineral calcium, bone mineral density and osteocalcin were detected in the drip milk or formula-fed infants. However, no clinical data on fractures or clinical evidence of rickets were reported.

Two trials in infants weighing <1600 g at birth examined the impacts of unsupplemented term donor or formula milk on feed

intolerance (*176*, *177*). Both trials had small sample sizes and small numbers of actual events and reported no significant differences between the feeding groups. No statistically significant differences were found even when these data were combined in a meta-analysis (Level I evidence) (*18*) (see summary Table 2.1.5).

## Conclusions and implications

Available data from meta-analyses and RCTs indicate that feeding with donor human milk rather than pre-term or standard infant formula may reduce the incidence of necrotising enterocolitis in pre-term infants. There are insufficient data to conclude if there are neurodevelopmental advantages associated with donor human milk compared with pre-term formula, although there is some evidence that donor milk is better than standard infant formula. Growth was slower in the short term in the infants who were fed donor milk than those fed formula. There are insufficient data to assess the effects on long-term growth outcomes or feed intolerance in small LBW infants.

Most studies comparing donor human milk with artificial formula milk that were identified had design features that limit their current clinical significance. The trials were small and unblinded. Most of these studies used donor drip milk, which is predominantly fore milk and has a lower calorie density than hind milk. Further, all but one of the studies was initiated over 20 years ago. Since then, there have been significant changes in the management of pre-term infants, including availability of formula milk adapted for pre-term infants and nutrient fortifiers for human milk. No evidence relating to micronutrient deficiencies was located. Overall, the available evidence suggests that providing LBW infants with donor milk rather than formula, particularly standard infant formula, may result in some advantages to the infant.

### Infants <32 weeks gestation (or birth weights <1500 g if gestation is not available)

The majority of infants included in the studies were in this group of LBW infants and the above results apply to them. Although there is some indication of a lower incidence of necrotising enterocolitis in infants fed donor human milk, there is insufficient evidence to conclude whether there are any neurodevelopmental advantages. Growth in the neonatal period is slower in the short term in infants fed donor human milk compared with formula milk, but there are insufficient data to assess the effects on long-term growth outcomes.

### Infants 32–36 weeks gestation (or birth weights 1500–2000 g if gestation is not available)

This group of LBW infants accounted for a small proportion of the subjects in the identified studies. In the absence of more evidence, it can be assumed that the findings in this group were similar to those in infants <32 weeks gestation.

### Term LBW infants (or birth weights >2000 g if gestation is not available)

There were no data on outcomes in this subgroup of LBW infants.

Almost all studies included in this section were conducted in developed countries. Although the results are unlikely to be different in developing country settings, greater efforts would be required in developing countries to establish and maintain donor milk banks according to international standards. This may not be feasible in primary healthcare settings and in small hospitals in developing countries.

## Recommendations

Many international and national organizations strongly support the provision of pasteurized donor milk to LBW infants. In contrast, many developed country neonatal units preferentially provide artificial infant formula rather than donor human milk to LBW infants.

Donor human milk may be a feasible option in many developing countries and should be considered as an important alternative to artificial infant formula. Feasibility of providing donor human milk is influenced by the amount that can be expressed by mothers and the availability of donor banks. Equipment and training for heat treatment and milk banking may be difficult to obtain in some countries. The findings from this review support these recommendations.

**SUMMARY TABLE 2.1.3**
**Effects of donor human milk compared with formula feeding on infection or necrotising enterocolitis in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| McGuire & Anthony (*174*) Meta-analysis of RCTs (LI) | Birth weight <1850 g. Allocated to milk feeds as sole diet | 65% | 35% | None | Unsupplemented term or pre-term drip breastmilk only (n=167) *compared with* standard or pre-term infant formula (n=176) | Possible necrotising enterocolitis | RR 0.34 [0.12, 0.99] |
| | | | | | | Confirmed necrotising enterocolitis | RR 0.25 [0.06, 0.98] |
| Schanler et al (*178*) RCT (LII) | Gestation <30 weeks. Mothers who intended to breastfeed. | 100% | None | None | If supply of own mother's milk was insufficient, infants were provided with at least 50 ml/kg of supplemented pasteurized donor milk (n=81) *compared with* pre-term formula (n=92) from birth to day 90. | Septicaemia | OR 1.04 [0.53, 2.05] |
| | | | | | | Confirmed necrotising enterocolitis | RR 0.53 [0.14, 1.82] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation and those weighing 2001–2500 g to have a gestation of 37 weeks or more

### SUMMARY TABLE 2.1.4
### Effects of donor human milk compared with formula feeding on neurodevelopment in LBW infants

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Lucas et al (*16*) RCT (LII) | Birth weight <1850 g, received feed as sole diet | 60% | 40% | None | Unsupplemented term drip breast milk (n=62) *compared with* pre-term formula (n=52) | Bayley psychomotor development index score at 18 months | WMD 1.20 [-4.4, 6.8] |
| | | | | | | Bayley mental development index score at 18 months | WMD 0.5 [-6.2, 7.1] |
| Tyson et al (*177*) RCT (LII) | Birth weight <1500 g, received feed as sole diet | 100% | None | None | Unsupplemented term drip breast milk (n=34) *compared with* pre-term formula (n=42) | Brazelton neonatal behavioural assessment scale (response to inanimate objects) at 37 weeks gestational age | WMD -2.50 [-3.65, -1.35] |
| | | | | | | Brazelton neonatal behavioural assessment scale (response to auditory and visual stimuli) at 37 weeks gestational age | WMD -0.80 [-1.34, -0.26] |
| Lucas et al (*16*) Cohort (LIII-2) non-random comparison within two RCTs | Birth weight <1850 g, received feed as sole diet | 70% | 30% | None | Standard infant formula only (n=55) *compared with* unsupplemented term drip breast milk only (n=62) | Bayley psychomotor development index score at 18 months | WMD 8.8 [3.3, 14.3] |
| | | | | | | Bayley mental development index score at 18 months | WMD 2.1 [-4.4, 8.7] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

### SUMMARY TABLE 2.1.5
### Effects of donor human milk compared with formula feeding on feed tolerance in LBW infants

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Henderson et al (*18*) Meta-analysis of RCTs (LI) | Birth weight <1600 g, received feed as sole diet | 95% | 5% | None | Unsupplemented term drip breast milk (n=58) *compared with* standard infant formula (n = 70) | Feed intolerance by hospital discharge | RR 0.30 [0.07, 1.37] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## (3) OPTIMAL DURATION OF EXCLUSIVE BREASTFEEDING

### Results

Exclusive breastfeeding (EBF) is now recommended for all infants for the first 6 months of life. A systematic review on the optimal duration of exclusive breastfeeding (*145*) cautioned that further research was required to rule out small adverse effects on the risk of malnutrition, including micronutrient deficiencies, especially in susceptible infants. We summarize here the available evidence for optimal duration of EBF in LBW infants, including a few papers published after the systematic review.

#### Effects on mortality and serious morbidities

No studies were located which directly examined the impact of EBF duration on mortality or serious morbidity in LBW infants. Bhandari et al evaluated the effect of community-based promotion of EBF for the first 6 months of life on diarrhoeal illness and growth in a rural population in Haryana, India (*187*). In a subgroup analysis, they examined the effect of EBF promotion among LBW infants. The intervention resulted in a substantially higher proportion of LBW infants exclusively breastfed at 3 months (79% and 40% in the intervention and control groups, respectively) and in the sixth month (41% and 4% in the intervention and control groups, respectively). At the 6-month visit, the prevalence of diarrhoea in the previous 7 days was not significantly lower in the intervention compared with the control group (OR 0.88, 95%CI 0.72 to 0.99). The proportion of children who had an episode of diarrhoea in the previous 3 months for which treatment was sought outside home was also not significantly different between the groups (OR 0.73, 95%CI 0.41 to 1.40) (N. Bhandari, unpublished data 2005). However, these effect sizes were similar to those reported previously for all enrolled infants, and the lack of significance for the LBW subgroup could have been due to insufficient statistical power.

#### Effects on neurodevelopment

Only one study which evaluated the neurodevelopmental impacts of EBF duration in LBW infants was located and is summarized in Table 2.1.6 (Level II evidence) (*188*). This study was one of a series of RCTs conducted in Honduras. In this trial, Dewey et al randomized term exclusively breastfed SGA infants to receive either complementary foods at 4 months of age while continuing to breastfeed at the usual frequency; or to continue EBF until 6 months of age and then receive complementary foods. The complementary foods were hygienically prepared and provided twice daily. This study reported no significant differences in motor development at 12 months of chronological age. However, neither the parents nor the fieldworkers were blinded to the group assignment, neurodevelopmental outcomes were limited to parental reports and no validation was attempted. It is also likely that this study was significantly underpowered.

#### Effects on malnutrition

Impacts of EBF duration on growth were examined in three trials (Level II evidence) (*187*, *189*, *190*), which are summarized in Table 2.1.7.

The trial in term SGA infants by Dewey et al and subgroup analysis of LBW infants in the trial by Bhandari et al are described above (*187*, *189*). Marriott et al randomized pre-term infants in the UK to two groups: one group introduced solid foods at 2.8 months while continuing to breastfeed at the usual frequency; the other continued breastfeeding until 5 months chronological age and then introduced solid foods (*190*). However, this was a multifaceted intervention. The early weaning group were also provided with instructions on how to feed their infants a high protein and high carbohydrate solid food diet. The late weaning group was advised to feed their infants according to standard UK recommendations. All infants in the study were provided with supplemental iron and vitamins and were followed until 12 months of chronological age. Investigators, but not the participants, were blinded to the allocations.

Dewey et al reported no significant differences in the impact of EBF up to 4 months compared to 6 months on change in weight, length, and head circumference till 6 months of age, even in the subgroup of term SGA infants whose mothers had a low body mass index (*189*). Marriot reported a significantly greater rate of increase in length in the group provided with solid foods at 2.8 months rather than 5 months, but no difference in weight or head circumference (*190*). Infants who commenced solid foods at 2.8 months had slightly higher 12-month mean length z scores, compared to the infants who commenced solid foods at 5 months. No significant differences in head circumference or weight-for-age z scores at 12 months were reported. Bhandari et al reported no significant differences in mean weight, mean length and the proportion of wasted or stunted infants at 6 months of age (*187*). The confidence intervals were fairly narrow and rule out large differences between the study groups. However, while interpreting these results it should be considered that not all LBW infants in the intervention group were exclusively breastfed until 6 months of age (79% at 3 months and 41% at 6 months).

### Effects on other important outcomes

Two RCTs were located which examined the impact of EBF duration on rates of *iron-deficiency anaemia* (Level II evidence) (*189–191*). These trials are described above and summarized in Table 2.1.8. Marriott et al reported that pre-term infants who commenced a high protein, high carbohydrate diet at 2.8 months had slightly higher haemoglobin levels compared to the infants who commenced standard solid foods at 5 months (*190*). In contrast, Dewey et al detected no significant differences in mean haemoglobin, mean haematocrit concentrations or rates of anaemia at 6 months in term SGA infants fed complementary foods at 4 months versus 6 months (*189*). However, it is unclear if this analysis was an *a priori* prespecified hypothesis and if the sample size was truly adequate to detect a significant difference. In a recent re-analysis of the Honduras trial, Dewey et al reported a significant interaction between the intervention group allocation (EBF or solid foods) and iron supplementation during 4–6 months (based on haemoglobin status at baseline, i.e. 4 months of age) (*191*). In the subgroup of infants who received iron supplements, EBF infants had significantly higher mean haemoglobin levels. On the other hand, in the subgroup of infants who did not receive iron supplements, EBF infants had significantly lower mean haemoglobin levels. Considering that infants given iron supplements did not benefit from complementary foods at 4–6 months, the authors concluded that EBF for 6 months (with iron supplementation) can be recommended for term LBW infants.

## Conclusions and implications

There are limited data on the optimal duration of EBF in LBW infants. The three RCTs identified did not measure the effect of EBF duration on mortality and morbidity and only one trial reported the effects on neurodevelopment. The sample sizes of two of these studies were small. Contrary to other issues, most studies were conducted in term, SGA infants in developing country settings.

### Infants <32 weeks gestation (or birth weights <1500 g if gestation is not available)

In this group of LBW infants, the data from the one available trial from the UK suggested that early supplementation of breastfeeding (at about 3 months of age) with a high calorie diet may result in marginally higher length-for-age z scores and haemoglobin levels. No data are available for other key outcomes. Overall there is insufficient evidence to recommend a specific EBF duration in these infants.

### Infants 32–36 weeks gestation (or birth weights 1500–2000 g if gestation is not available)

The conclusions for this group of LBW infants are similar to those <32 weeks gestation with regard to growth and haemoglobin levels. No data are available for other key outcomes.

Overall, there is insufficient evidence to recommend a specific EBF duration in these infants.

### Term LBW infants (or birth weights >2000 g if gestation is not available)

In this group of LBW infants, the available evidence from two trials suggested that EBF to 6 months, compared to 4 months, had no deleterious impact on neurodevelopment, growth or haemoglobin levels (with iron supplementation). Although there is still insufficient evidence to draw firm conclusions, EBF for 6 months for term LBW infants seems to be safe and could be associated with lower morbidity.

Although the available data are limited, most of the studies were conducted in developing country settings; the findings are therefore directly applicable to those settings.

## Recommendations

No specific recommendations for LBW infants from expert groups were located. Standard practice in neonatal units is to recommend EBF with supplemental vitamins and minerals for all LBW infants until 6 months chronological age. This review supports these recommendations.

**SUMMARY TABLE 2.1.6**
**Effect of exclusive breastfeeding (EBF) duration on neurodevelopment in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Dewey et al (*188*)<br>RCT<br>(LII)<br>Subgroup analysis | SGA term infants with birth weight 1500–2400 g. | None | None | 100% | EBF until 6 months (n=56) *compared with* EBF until 4 months (n=52). | Motor development as assessed by parent (1 month recall) | |
| | | | | | | – Age (months) when able to crawl | MD[b] -0.60 [-1.30, 0.1] |
| | | | | | | – Age (months) when able to sit from lying position | MD[b] -0.60 [-1.22, 0.02] |
| | | | | | | – % able to walk by 12 months | Adjusted[b] RR 0.68 [0.32, 1.44] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

[b] Adjusted for birth weight, weight gain from 0-6 months and months of reported prenatal iron supplementation.

**SUMMARY TABLE 2.1.7**
**Effect of exclusive breastfeeding (EBF) duration on growth outcomes in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Marriot et al (*190*) RCT (LII) | <37 weeks gestation and <2200 g at birth | 50% | 50% | None | Any milk feeding (breast or formula) until 5 months when standard weaning foods were introduced (n=29) *compared with* any milk feeding (breast or formula) until 2.8 months when high calorie weaning foods were introduced (n=36) | Length standard deviation scores at 12 months corrected age | WMD -0.3 [-0.7, -0.2] |
| | | | | | | Weight standard deviation scores at 12 months corrected age | WMD -0.1 [-0.3, 0.2] |
| | | | | | | Head circum-ference standard deviation scores at 12 months corrected age | WMD 0.0 [-0.2, 0.2] |
| Bhandari et al (*187*) Cluster RCT (LII) Subgroup analysis | Subgroup of LBW infants (<2500 g at birth) | <1% | 15% | 85% | *Subgroup of LBW infants in:* Intervention group (community promotion of EBF for 6 mo) [n=159] *compared with* control group [n=124] | Weight (kg) at 6 mo | Adjusted[b] MD -0.02 [-0.12, 0.08] |
| | | | | | | Length (cm) at 6 mo | -0.20 [-0.66, 0.25] |
| | | | | | | % stunted | Adjusted[b] difference in proportions 9% (-2% to 20%) |
| | | | | | | % wasted | -2% (-6% to 1%) |
| | | | | | *[EBF rates at 3 mo:* Intervention: 79%, Control: 40% (P<0.0001) *EBF rates at 6 mo:* Intervention: 41%, Control: 4% (P<0.0001)] | | |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.
[b] Adjusted for cluster randomization and mother working outside home.

**SUMMARY TABLE 2.1.8**
**Effect of exclusive breastfeeding (EBF) duration on iron deficiency anaemia in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Dewey et al (*189*) Sub analysis of RCT (LIII-1) | SGA term infants birth weight 1500–2400 g, EBF until 4 months | None | None | 100% | EBF until 6 months (n=8) *compared with* EBF until 4 months (n=20) | Proportion of infants with haemoglobin <103 g/L at 6 months | Adjusted difference in proportions[b] 2% [-39%, 42%] |
| | | | | | | Proportion of infants with haematocrit <0.33 at 6 months | 0% [-41%, 41%] |
| | | | | | | Proportion of infants with ferritin <12 µg/L at 6 months | 31% [-6%, 68%] |
| Dewey et al (*191*) RCT (LII) Subgroup analysis | SGA term infants birth weight 1500–2400 g, EBF until 4 months | None | None | 100% | **Among infants who received iron supplementation from 4–6 mo:** EBF until 6 mo (n=10) *compared with* solid foods group (n=14) | Haemoglobin (g/L) at 6 months chronological age | MD 6.8 g/L [0.1, 13.5] |
| | | | | | **Among infants who did not receive iron supplementation from 4–6 mo:** EBF until 6 mo (n=47) *compared with* solid foods group (n=45) | Haemoglobin (g/L) at 6 months chronological age | MD -5.1 g/L [-8.1, -2.1] |
| Marriot et al (*190*) RCT (LII) | <37 weeks gestation and <2200 g at birth | 50% | 50% | None | Any milk feeding (breast or formula) until 5 months when standard weaning foods were introduced (n=29) *compared with* any milk feeding (breast or formula) until 2.8 months when high calorie weaning foods were introduced (n=36) | Haemoglobin (g/L) at 6 months corrected age | MD -6 [-10.63, -1.37] |
| | | | | | | Serum ferritin (ng/ml) at 6 months corrected age | MD -1.5 [-2.93, -0.07] |
| | | | | | | Serum iron (µmol/l) at 6 months corrected age | MD -2.8 [-3.25, -2.35] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.
[b] Adjusted for birth weight, weight gain from 0-6 months and months of reported prenatal iron supplementation.

## 2.2 Human milk supplementation

Provision of nutrient supplements to human-milk-fed LBW infants is common in developed countries because they are perceived to have clinical benefits. In this section, the efficacy and safety of the most commonly used nutrient supplements are reviewed:

- Individual vitamins or minerals
  - — Vitamin A
  - — Vitamin D
  - — Vitamin K
  - — Iron
  - — Zinc
  - — Calcium and phosphorus
- Multivitamins
- Multicomponent fortifiers.

### VITAMIN A SUPPLEMENTATION

No studies were found that evaluated the efficacy of a daily supplement of 700–1500 IU per kg body weight of vitamin A on mortality, morbidity, development or growth in LBW infants. An alternative approach, in some developing countries, provided 1–3 large doses (each dose 25,000 to 50,000 IU) of vitamin A in the first few days of life. Four trials were located which examined the impacts of large-dose vitamin A supplementation in the first few days of life on mortality rates in human-milk-fed LBW infants (*192–195*).

#### Results

##### Effect on mortality

Details of the study design, participants and the interventions and results for three trials are summarized in Table 2.2.1 (*192–194*). All of these studies were individually randomized, double blind, placebo-controlled trials. Two of them had very low power to detect any reasonable differences in mortality in LBW infants (*192–193*). The study by Rahmathullah et al was larger and showed a significant 37% reduction in mortality during the first 6 months of life in the vitamin A supplemented group of LBW infants (see summary Table 2.2.1) (*194*). Interestingly, Rahmathullah et al found no difference in mortality among the subgroup of infants with normal birth weight (RR 1.03, 95%CI 0.75 to 1.42), but Humphrey et al reported a significant difference in mortality in normal birth weight infants (RR 0.09, 95%CI 0.01 to 0.70) (*194*, *193*).

In addition, Malaba et al recently published a similar study to that of Rahmathullah et al by examining the impacts of 50,000 IU of vitamin A within 96 hours of delivery in HIV-negative women in Zimbabwe (*195*). Subgroup analysis was performed for 1108 LBW infants, but limited data were presented in the paper. Neonatal mortality was reported to decrease by at least 20% in LBW infants (RR <0.8); the results were presented pictorially and no proportions or confidence intervals were provided. The authors state that high-dose vitamin A supplementation significantly reduced the mortality in LBW infants but there was a non-significant trend to increased mortality in non-LBW infants.

##### Effect on morbidity

Coutsoudis et al reported no significant impact of neonatal vitamin A supplementation on the incidence of respiratory distress in the neonatal period (RR 0.95, 95%CI 0.69 to 1.30). However, the sample size was too small to detect even moderate differences in morbidity between the groups. There was a trend towards increased hospitalization for pneumonia during the first year of life in the vitamin A group (RR 3.74, 95%CI 0.82 to 17.0). This difference was statistically not significant after adjusting for risk factors of pneumonia (P=0.19 from proportional hazards model) (*192*).

Humphrey et al found no effect of vitamin A supplementation on one-week period prevalence of common morbidities at 4, 6 or 12 months of age. However, between birth and 4 months of age they reported that a lower proportion of infants were brought for medical care and treatment of cough in the vitamin A group (14.2% vs. 24.6%, RR 0.58, 95%CI 0.38 to 0.87) (*193*).

##### Effect on neurodevelopment, malnutrition or other outcomes

No studies examining the effect of vitamin A supplementation in LBW infants on neu-

rodevelopment or malnutrition were located. Coutsoudis et al (n = 43 supplemented LBW infants) and Rahmathullah et al (n = 1851 supplemented LBW infants) reported no episodes of bulging fontanelle or other neurological adverse effects associated with vitamin A supplementation (*192*, *194*).

## Conclusions and implications

There is paucity of evidence that the usually recommended daily dose of 700–1500 IU per kg body weight is efficacious in LBW infants. Further, there are no data to compare large-dose supplementation in the first few days of life with a small daily dose of vitamin A.

There is evidence from one study in India that a large dose of vitamin A (50,000 IU in one or two divided doses) during the first days of life may have a survival advantage, particularly in infants with birth weight <2000 g. This finding needs to be confirmed in other studies in developing country settings before this intervention can be recommended for LBW infants.

## Recommendations

International and national organizations recommend a daily vitamin A supplementation of 700–1500 IU per kg body weight from birth until the infant attains 2000 g body weight to growing pre-term infants receiving human milk. Standard practice in many neonatal units is to provide commercially manufactured multivitamin preparations, which include vitamin A, to LBW infants receiving unfortified human milk from birth until the infant attains 2000 g body weight. It was not possible to provide additional recommendations due to insufficient evidence.

**SUMMARY TABLE 2.2.1**
**Effect of vitamin A supplementation on mortality**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Humphrey et al (*193*) RCT (LII) | Subgroup analysis limited to infants with birth weight 1500–2499 g | NK | NK | 76% | Infants who received 50,000 IU Vitamin A on the first day of life (n=101) *compared with* infants who received placebo (n=98) | Mortality during the first year of life | RR 0.74 (0.26, 2.02) |
| Coutsoudis et al (*192*) RCT (LII) | Gestational age <36 weeks and birth weight 950–1700 g | 50% | 50% | None | Infants who received 3 doses of 25,000 IU Vitamin A each before day 10 of age (n=43) *compared with* infants who received placebo (n=46) | Mortality during the first year of life | RR 1.07 (0.16, 7.26) |
| Rahmathullah et al (*194*) RCT (LII) | Subgroup analysis limited to infants with birth weight <2500 g | 3% | 15% | 82% | Infants who received 2 doses of 24,000 IU Vitamin A each on days 1 and 2 of age (n=1851) *compared with* infants who received placebo (n=1820) | Mortality during the first 6 months of life | Overall RR 0.63 (0.48, 0.83)<br>*Birth weight* <2000g RR 0.48 (0.33, 0.69)<br>*Birth weight* 2000–2499 g RR 0.76 (0.52, 1.10) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## VITAMIN D SUPPLEMENTATION

The vitamin D content of a typical oral multivitamin supplement used for pre-term infants receiving human milk is 400 IU per daily dose.

### Results

#### Effect on mortality, morbidity and neurodevelopment

No intervention studies were located which examined the impact of vitamin D supplementation on mortality rates, morbidity or development in LBW infants.

#### Effect on bone mineralization

No studies were located which examined the impact and clinical outcomes in infants who were fed unsupplemented and vitamin D-supplemented human milk. Studies reporting clinical outcomes related to vitamin D supplementation have only involved case series and were from the early 1970s. Robertson reported on 25 South African pre-term infants of mean gestational age 31 weeks (mean birth weight 1100 g) who were fed unsupplemented mother's own milk from birth until hospital discharge (*173*). Lucas et al reported on 45 UK pre-term infants of mean gestational age 30 weeks (mean birth weight 1050 g) fed unsupplemented mother's own milk from birth until hospital discharge (*196*). In both these studies, the infants were followed from birth till hospital discharge; high rates of osteopenia and fractures in the infants fed unsupplemented human milk were reported. Lucas et al followed the infants further till 18 months of age and reported that infants fed unsupplemented pre-term mother's milk had 2 cm reduction in linear growth and two infants had clinical evidence of rickets.

Three studies were located which compared different doses of vitamin D on bone mineralization in human-milk-fed VLBW (very low birth weight, <1500 g) infants (*197–199*). Evans et al randomized 81 Canadian, breastfed LBW infants <1500 g and gave either the usual 400 IU dose or a high-dose (2000 international units (IU)) of vitamin D from 72 hours till 6 weeks postnatal age (*197*). At age 6 weeks, the radiographic bone scores (median 2.0 and 2.5 in high-dose and usual dose groups, respectively) as well as the mean serum osteocalcin concentrations were similar in the two study groups.

From 1985 to 1987 Backstrom et al randomized 70 infants <34 weeks gestational age (birth weight <2000 g) to receive vitamin D 500 IU or 1000 IU per day from the time of tolerance of full enteral nutrition until 3 months of age. This study had a factorial design and infants also received 108 mg/kg calcium with 53 mg/kg phosphorus or placebo. At 3 months of age the infants who received 500 IU vitamin D had a statistically significant higher bone mineral content than those infants who received 1000 IU. The lowest bone mineral content was found in infants who received 1000 IU/day vitamin D and no calcium or phosphorus. At 9–11 years, only 50% of infants (n=35) were available for follow-up; there was no difference in bone mineral content or bone mineral density between the infants who received low or high vitamin D doses (*198*).

In a later study (from May 1994 to January 1996), Backstrom et al randomized 39 infants <33 weeks gestational age and gave vitamin D 200 IU/kg of body weight/day (up to a maximum of 400 IU/day) or 960 IU/day until 3 months of age. There was no difference in bone mineral content or in bone mineral density at 3 and 6 months corrected age between the infants who received low or high vitamin D (*199*).

### Conclusions and implications

There is some evidence of the need for vitamin D supplementation of human-milk-fed infants <1500 g for adequate bone mineralization and to prevent rickets of prematurity. There seems to be no additional benefit of increasing the intake of vitamin D for VLBW infants from the usually recommended 400 IU per day. There are no clinical trial data on the effect of vitamin D on key clinical outcomes in infants with birth weight >1500 g. There are very few studies from developing countries where nutrient deficiencies may be more common.

### Recommendations

International and national organizations recommend daily vitamin D supplementation of 400 IU from birth until the infant attains 2000 g body weight to growing pre-term infants receiving human milk. Provision of 400 IU of vitamin D to LBW infants receiving human milk from birth until 6 months of chronological age has been standard practice in many developed country neonatal nurseries. Calcium and phosphorus supplementation are also recommended to ensure bone mineralization. It was not possible to provide additional recommendations due to insufficient evidence.

## VITAMIN K SUPPLEMENTATION

Intramuscular vitamin K is commonly administered in doses of 1 mg at birth to all infants over 1000 g and 0.3 mg/kg IM to infants weighing less than 1000 g at birth. Alternatively, oral vitamin K is administered 2 mg orally at birth, followed by 2 mg on day 3–5 and day 28.

### Results

#### Effect on mortality, neurodevelopment and malnutrition

No intervention studies were located which examined the impact of vitamin K supplementation on mortality rates or development in LBW infants.

#### Effect on serious morbidity

A systematic review of studies in term infants indicated that there was a significantly lower risk of bleeding during the first week of life (RR 0.73, 95%CI 0.56 to 0.96) and bleeding after circumcision (RR 0.18, 95%CI 0.08 to 0.42) in infants who received vitamin K on day 1 of life (*200*). Similarly, there are studies in term infants which examined a possible association of neonatal vitamin K supplementation with *childhood cancer*. In the early 1990s, Golding et al reported a statistically significant association between term infants from developed countries receiving IM vitamin K and an increased incidence of childhood cancer (*201*, *202*). However, seven other case-control studies found no relationship and three found a weak relationship between neonatal administration of IM or IV vitamin K and the risk of solid childhood tumours or leukaemia (*203*). A review of these studies concluded that the results did not establish a causal relationship between IM vitamin K and increased risk of childhood cancer (*203*).

#### Effect on other important outcomes

Three case series were located which examined the effect of vitamin K supplementation on *coagulation studies and plasma vitamin K levels* in VLBW infants receiving total parenteral nutrition (*204–206*). Infants were administered 1.0 mg/kg intramuscular vitamin K (*205*), 0.5–1.0 mg intramuscular vitamin K (*206*), or 2.0 mg enteral vitamin K (*204*) within 48 hours of birth. Normal coagulation status was reported in all three studies. Kumar et al and Costakos et al reported high vitamin K levels in infants <1000 g given 1.0 mg intramuscular vitamin K and suggested decreasing the amount of vitamin K in total parenteral nutrition (TPN) and maintaining the intramuscular dose of vitamin K in infants under 1000 g to 0.3 mg/kg. No studies examined the impacts in infants who received no TPN. Human milk intake was also not recorded.

### Conclusions and implications

There is little evidence of the efficacy of vitamin K supplementation in LBW infants. Currently, there are no data to suggest that the effects of vitamin K supplementation would be different from those in term AGA infants.

### Recommendations

Policy statements from international and national organizations state the importance of administering IM or oral vitamin K at birth for LBW infants. Standard practice in many neonatal units is to administer 1 mg intramuscular vitamin K at birth for infants weighing 1000 g or more at birth and 0.3 mg/kg intramuscular vitamin K for infants with birth weights less than 1000 g. If oral vitamin K is administered, it is provided in a dose of

2 mg orally at birth, followed by 2 mg on day 3–5 and day 28. Additional recommendations could not be provided due to insufficient evidence.

## IRON SUPPLEMENTATION

Iron supplementation is usually provided to LBW infants as 2–3 mg/kg/day ferrous fumarate or ferrous gluconate from 2 to 8 weeks of age until 12 months of age.

### Results

#### Effects on mortality, neurodevelopment and malnutrition

No studies were located which examined the impact of oral iron supplementation on mortality, neurodevelopment and malnutrition in human-milk-fed LBW infants.

#### Effects on iron status

A number of RCTs examined the impact of giving iron supplements to LBW infants on the rates of iron-deficiency anaemia (IDA). Most trials were conducted in the 1960s and 1970s (*163*, *207–210*). Only one of these studies examined the impact of oral iron supplementation in breastfed pre-term infants (*208*) (see summary Table 2.2.2). In this study, Lundstrom et al randomized 117 Finnish infants who weighed less than 2000 g at birth (mean birth weight 1650 g) to receive 2 mg/kg/day of oral iron or no iron supplementation from 2 weeks to 6 months of chronological age. Significant improvements in mean haemoglobin were demonstrated at 2 months, 3 months and 6 months of chronological age in the supplemented group. At 6 months the improvement in mean haemoglobin was 10 g/l. In addition, 77% of breastfed infants who had never received iron supplementation became anaemic by 6 months of age, compared to 0% in the supplemented group. No long-term effects have been reported. One study was identified which examined the impacts in term LBW infants (*211*) (see summary Table 2.2.2). In this study, Aggarwal et al randomized 73 breastfed Indian infants who were term LBW (mean birth weight 2290 g) to receive 3 mg/kg/day of oral iron or no iron supplementation from 50 to 80 days of age. Significant improvements in mean haemoglobin were demonstrated at 4 and 8 weeks of age in the supplemented group; however, by 8 weeks of age 65% of the infants were lost to follow up (n=26 at 8 weeks of age).

Other studies have examined the optimal time to commence iron supplementation in AGA pre-term infants (*191*, *212*, *213*). Franz et al examined the impact of enteral iron supplementation in 133 German infants weighing <1300 g at birth. Infants were randomized to receive either 2 mg/kg/day oral iron as soon as enteral feedings of >100 ml/kg/day were tolerated (early enteral iron supplementation) or 2 mg/kg/day oral iron at 61 days of life (late enteral iron supplementation) (*212*). He reported that infants in the late initiation group were more often iron-deficient by day 61 of life (26/65 vs. 10/68; RR 2.72, 95%CI 1.43 to 5.18) and received more blood transfusions after day 14 of life (see summary Table 2.2.2). Siimes also examined the rates of iron-deficiency anaemia in 67 Scandinavian breastfed infants (30–36 weeks gestation and 1000–2400 g birth weight) over a 12-month period and reported high rates of anaemia when unsupplemented LBW infants exceeded 6 months of chronological age (*213*). A study in term LBW breastfed infants in Honduras reported that 47.7% of infants had a haemoglobin concentration <100g/l at 2 months of age (*191*).

#### Impacts on other important outcomes

Four studies were also located which examined the impacts of iron supplementation on iron metabolism and toxicity (*208*, *212*, *214*, *215*). Studies of Franz et al (*212*) and Lundstrom et al (*208*) are described above. Scott et al (*215*) and Lackmann et al (*214*) examined the metabolism of iron in pre-term infants <2500 g in two small US case series. No adverse reactions to the administration of 2–3 mg/kg/day of oral iron supplementation were reported in any study. Scott et al and Lackmann et al both reported that pre-term infants have limited iron-binding capacity and that the therapeutic: toxic ratio for iron is narrower than for most other nutrients.

## Conclusions and implications

There is evidence from developed and some developing countries that iron supplementation, started around 6–8 weeks of age in LBW infants, is effective in preventing anaemia during infancy. There is some evidence that anaemia is common in LBW infants fed unsupplemented human milk even at 8 weeks of age. There is also some evidence to suggest that iron supplementation, started at 2 weeks of age, may prevent this early anaemia in infants with birth weight <1500 g. However, the data are insufficient on the safety of iron supplementation during the first 2 months of life. There are no data on the effects of iron supplementation on mortality, common childhood illnesses or neurodevelopment in LBW infants.

## Recommendations

International and national organizations recommend the administration of supplemental oral iron to pre-term and SGA infants. Standard practice in neonatal units is to provide ferrous fumarate or ferrous gluconate at 2–3 mg/kg/day to LBW infants receiving unfortified human milk from 6–8 weeks of age until 12 months of chronological age. The findings of this review support these recommendations.

**SUMMARY TABLE 2.2.2**
**Effect of iron supplementation of breastfed LBW infants on iron status in the first 6 months of life.**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Lundström et al (*208*) RCT (LII) | Infants 1000–2000 g at birth | 30% | 70% | None | Infants who received 2 mg/kg/day elemental iron starting at 2 weeks of age (n=60) *compared with* infants who received no iron unless they developed anaemia (n=57) | Difference in proportion of infants who became anaemic by 6 months of age | -77% (-88%, -66%) |
| Aggarwal et al (*211*) RCT (LII) | Term LBW infants < 2500 g | None | None | 100% | Infants who received 3 mg/kg/day elemental iron from age 50–80 days (n=37) *compared with* infants who received placebo (n=36) | Adjusted haemoglobin change at 4 weeks | 4.6 g/l (0.5, 8.8) |
| | | | | | | Adjusted haemoglobin change at 8 weeks | 8.6 g/l (1.8, 15.4) |
| Franz et al (*212*) RCT (LII) | Infants <1301 g at birth | 100% | None | None | Infants who received 2 to 6 mg/kg/day elemental iron as soon as enteral feedings were fully tolerated (n=68) *compared with* infants who started receiving iron supplements only at 61 days of age (n=65) | Proportion of infants iron-deficient at 2 months age | -25% (-40%, -11%) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## ZINC SUPPLEMENTATION

### Results

#### Effect on mortality

One trial, which examined the impacts of zinc supplementation on mortality rates in SGA term infants, was identified (see summary Table 2.2.3) (*216*). No trials which examined the impacts in pre-term infants were located. Sazawal et al randomized 1154 term SGA infants in south India who were receiving human milk to either a zinc supplementation group (each infant receiving a supplement containing zinc 5 mg/d, riboflavin 0.5 mg/d, calcium 180 mg/d, phosphorus 90 mg/d, iron 10 mg/d and folate 60 µmol/d) or a control group (each infant receiving a supplement that did not contain zinc but contained other micronutrients as in the intervention group above). The supplementation commenced on day 15 of age and reached the full treatment doses as outlined above by 30 days of age; daily supplementation was given until the infant reached 12 months of chronological age. In this trial Sazawal et al reported that SGA term infants who received zinc supplementation had a statistically significant 70% reduction in mortality compared to the control group (RR 0.32; 95%CI 0.12 to 0.89).

#### Effect on serious morbidity

Two trials were located which examined the impacts on clinical illness (diarrhoea, acute respiratory infection) (see summary Table 2.2.4) (*217*, *218*). In one trial, 137 Brazilian term SGA infants (1500–2400 g) who were receiving human milk were randomized to receive either 5 mg zinc per day for 8 weeks or a placebo, with follow-up until they reached 6 months of age (*217*). Zinc supplementation was associated with a statistically significant 28% reduction in diarrhoeal prevalence and a 33% reduction in the prevalence of cough over the 6-month follow-up period. In the other trial, 100 south Indian LBW infants (1500–2400 g) who were receiving human milk were randomized to receive either 5 mg/day elemental zinc in a vitamin B complex syrup (n=50) or vitamin B complex syrup only (n=50) from birth until 12 months of chronological age (*218*). Zinc supplementation was associated with a statistically significant 29% reduction in diarrhoeal incidence over the 12-month follow-up period.

#### Effect on neurodevelopment

Two trials were located which examined the impacts on neurodevelopment (see summary Table 2.2.5) (*219*, *220*). In one trial, 200 term SGA infants from Delhi, India, who were receiving human milk were randomized to receive either a daily micronutrient supplement mix (folate, iron, calcium, phosphorus, and riboflavin) together with 5 mg/day of elemental zinc (n=100) or a micronutrient supplement mix without additional zinc (n=100) from day 30 to 9 months of chronological age (*219*). There was no significant effect of zinc on any of the measures of development or behaviour at 6 and 10 month evaluation. The second trial, in Brazil, which examined the impact of zinc supplementation on neurodevelopment in term SGA infants (see summary Table 2.2.5) (*220*), reported no significant differences in mental, psychomotor or behavioural development at 6 and 12 months of chronological age, as assessed by Bayley's Scales of Infant Development.

#### Effect on malnutrition

Three trials were located which examined the impacts on growth outcomes in term SGA infants (see summary Table 2.2.6) (*217*, *218*, *221*). In a Brazilian trial, Lira et al reported that zinc supplementation of 5 mg from birth until 8 weeks chronological age had no significant effect on weight and length gains from 0 to 26 weeks (*217*). In Chile, Castillo-Duran et al randomized 68 term SGA infants (mean birth weight 2300 ± 200 g, mean gestational age 39.1 ± 0.8 weeks, 29/68 breastfed) who were receiving human milk to receive either 5 mg zinc per day for 6 months or a placebo (*221*). He reported statistically significant improvements in weight-for-age and length-for-age z scores in zinc supplemented infants at 6 months of age. No trials reported the impact on standard deviation scores or malnutrition

## SUMMARY TABLE 2.2.3
## Effect of zinc supplementation of breastfed LBW infants on mortality

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Sazawal et al (*216*) RCT (LII) | Full term SGA infants | None | None | 100% | Infants who received 5 mg/day elemental zinc from 1 to 9 months of age (n=581) *compared with* infants who received no zinc (n=573) | Infant deaths between 1 and 9 months of age | RR 0.32 (0.12, 0.89) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## SUMMARY TABLE 2.2.4
## Effect of zinc supplementation of breastfed LBW infants on serious morbidity

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Lira et al (*217*) RCT (LII) | Full term SGA infants | None | None | 100% | Infants who received 5 mg/day elemental zinc daily for 8 weeks (n=71) *compared with* infants who received placebo (n=66) | Prevalence of diarrhoea (0–26 weeks) | Adjusted[b] prevalence ratio 0.72 (0.52, 0.99) |
| | | | | | | Prevalence of cough (0–26 weeks) | Adjusted[b] prevalence ratio 0.67 (0.44, 1.04) |
| Sur et al (*218*) RCT (LII) | LBW | None | 50% | 50% | Infants who received 5 mg/day elemental zinc in a vitamin B complex syrup from birth until 12 months of chronological age (n=50) *compared with* infants who received vitamin B complex syrup only (n=50) | Diarrhoeal incidence over first 12 months | RR 0.71 (0.5, 0.98) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

[b] Adjusted for water supply

rates. In a trial on Indian infants, a statistically significant improvement in weight-for-age z score at 12 months of age was reported in the infants who received zinc supplements (–1.45 ± 0.95 compared to –2.17 ± 0.90, p <0.001). Significant gains in mean length and weight were also reported (*218*).

### Effect on other important outcomes

In one trial in pre-term infants in a developed country which examined the effect of zinc supplementation on *zinc status* (*222*), 25 Canadian infants under 32 weeks gestation (mean gestational age 29.9 weeks, mean birth weight 1310 g) were randomized to receive either mother's milk supplemented with multicomponent human milk fortifier (providing 1.8 mg/kg/day of oral zinc sulfate) or mother's milk supplemented with calcium and phosphorus alone from birth until discharge from hospital. Reporting that pre-term infants who were fed their mother's milk, with or without zinc supplementation, maintained normal zinc levels from the time of hospital discharge till 12 months of chronological age, the authors concluded that supplemental zinc either in hospital or post-hospital discharge did not appear to be required for preterm infants fed their mother's milk. However, plasma zinc levels are a poor measure of zinc status and therefore supplementation trials in premature infants would provide the best evidence of the role of zinc in their nutrition.

## Conclusions and implications

There are no data on the effect of zinc on key clinical outcomes in pre-term infants. Data from two trials in developing countries suggest that term LBW infants in developing countries may have lower mortality and morbidity if they receive zinc supplementation. There seems to be no evidence that zinc supplementation in these infants improves neurodevelopment or affects growth.

## Recommendations

No policy statements were available from international or national organizations on the use of zinc in the LBW infant. It is not standard practice in most neonatal units to provide zinc supplementation to LBW infants. However, it is standard practice in many neonatal units to give infants with birth weights less than 1500 g a multicomponent fortifier with human milk, which provides an additional 0.5–1.8 mg/kg/day of zinc until the infant reaches a weight of 1800–2000 g. Additional recommendations could not be provided due to lack of evidence.

## SUMMARY TABLE 2.2.5
## Effect of zinc supplementation of breastfed LBW infants on neurodevelopment

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Ashworth et al (*220*) RCT (LII) | Full term SGA infants | None | None | 100% | Infants who received 5 mg/day elemental zinc daily for 8 weeks (n=46) *compared with* infants who received placebo (n=44) | Bayley's Mental Development Index (MDI) scores at 6 months | MD -2.2 (-7.3, 2.9) |
| | | | | | | Bayley's Psychomotor Development Index (PDI) score at 12 months | MD -0.4 (-5.2, 4.4) |
| Black et al (*219*) RCT (LII) | Full term SGA infants | None | None | 100% | Infants who received 5 mg/day elemental zinc and a daily micronutrient supplement mix (folate, iron, calcium, phosphorus, and riboflavin) from 30 days to 9 months of age (n=100) *compared with* infants who received the micronutrient supplement mix but no zinc (n=100) | Bayley's Mental Development Index (MDI) scores at 6 months | Adjusted[b] regression coefficient 1.11 (-1.12, 4.16) |
| | | | | | | Bayley's Psychomotor Development Index (PDI) scores at 6 months | Adjusted[b] regression coefficient 2.94 (-0.68, 6.26) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

[b] Adjusted for birth weight, weight gained since birth, gender and socio-economic status

## SUMMARY TABLE 2.2.6
## Effect of zinc supplementation of breastfed LBW infants on growth outcomes

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Lira et al (*217*) RCT (LII) | Full term SGA infants | None | None | 100% | Infants who received 5 mg/day elemental zinc daily for 8 weeks (n=54) compared with infants who received placebo (n=54) | Weight gain (0–26 weeks), kg | MD 0.29 (-0.07 to 0.65) |
| | | | | | | Length gain (0–26 weeks), cm | MD 0.4 (-1.2, 0.4) |
| Castillo-Duran et al (*221*) RCT (LII) | Full term SGA infants | None | None | 100% | Breastfed infants who received 3 mg/day elemental zinc daily (n=20) compared with breastfed infants who received placebo (n=9) | Weight for age z-score at 6 months | MD 0.7 (0.15 to 1.25) |
| | | | | | | Length at 6 months, cm | MD 1.1 (-1.6, 3.8) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## CALCIUM AND PHOSPHORUS SUPPLEMENTATION

If calcium and phosphorus supplements are provided to LBW infants, they are often administered as individual supplements of calcium (2.0 mmol/kg/day) and phosphorus (0.5 mmol/kg/day) or in a multicomponent fortifier.

### Results

#### Effect on mortality, morbidity, neurodevelopment and malnutrition

No studies were located which examined the impact of calcium or phosphorus supplementation on mortality rates, serious clinical disease, neurodevelopment or malnutrition in LBW infants.

#### Effect on bone mineralization

A number of studies evaluated the short-term impacts of calcium and phosphorus supplementation in pre-term infants <33 weeks gestation; virtually all reported significant improvements in bone mineralization in supplemented infants up to 2 years of age (*223–230*). However, only three RCTs were located which examined the impact of calcium and phosphorus supplementation as individual components (not as part of multicomponent fortification) on longer-term bone mineralization (after 2 years of age) (*198*, *231*, *232*).

Only Backstrom et al compared the outcomes in supplemented and unsupplemented infants (198). From 1985 to 1987 he randomized 70 infants <34 weeks gestational age to receive 108 mg/kg calcium with 53 mg/kg phosphorus or a placebo from the time of tolerance of full enteral nutrition until the infant reached 3 months of age. This study had a factorial design and the infants also received vitamin D (500 IU or 1000 IU per day); this is described in the section on vitamin D. At 3 months of age the infants who received calcium and phosphorus supplementation had a statistically significant higher bone mineral content than those who received the placebo. The lowest bone mineral content was found in infants who received 1000 IU/day vitamin D and no calcium or phosphorus. At 9 to 11 years, only 50% of infants (n=35) were available for follow-up; no difference was found in bone mineral content or bone mineral density between the infants who received calcium and phosphorus supplementation and those on the placebo (*198*).

Laing et al randomized 74 US infants (birth weights <1500 g) receiving human milk to be given additional calcium and phosphorus supplements from birth until 47 days of age (*231*). The infants received either calcium 21 mmol/l (84 mg/dl) or calcium 31.2 mmol/l (125 mg/dl) and phosphorus 15.7 mmol/l (49 mg/dl). It was reported that both groups had no radiological evidence of rickets at 6 weeks chronological age. Combined calcium and phosphorus supplementation maintained plasma alkaline phosphatase activity within the normal range for age of 6 weeks.

Holland et al randomized 50 UK infants (birth weight <1250 g) to receive either 50 mg phosphate per day or a placebo from birth until discharge from hospital (*232*). No infant receiving phosphate supplements (50 mg per day) from birth until discharge had radiological evidence of rickets at the time of discharge; bone changes were apparent in 42% of the control group (risk difference [RD] 42%, 95%CI 19% to 64%).

In addition, a number of studies reported the beneficial effects of a long period of breastfeeding on bone mineral status in mineral-supplemented pre-term infants (*186*, *198*, *226*). In two studies, a dose response was apparent; the higher the breastmilk received, the higher the radial bone mineral content at 8–12 years of age (*186*, *226*).

### Conclusions and implications

There is some evidence that phosphorus and calcium supplementation reduces the risk of metabolic bone disease in pre-term infants and leads to short-term increases in bone mineralization in infants with gestation <32 weeks or birth weight <1500 g. There are no data on the effect of phosphorus and calcium supplementation on key clinical outcomes in infants with birth weight >1500 g. There are no studies from developing countries, where the prevalence of deficiency may be higher.

### Recommendations

International and national organizations describe the importance of providing phosphorus and/or calcium supplements to infants who weigh <1500 g at birth for improving bone mineralization and growth. Standard practice in many neonatal units is to give such infants calcium 2.0 mmol/kg/day and phosphorus 0.5 mmol/kg/day in addition to breastmilk until the infant attains a weight of 2000 g. The findings of this review support these recommendations.

## MULTIVITAMIN SUPPLEMENTATION

Neonatal multivitamin preparations commonly contain vitamins A, D, C, $B_1$, $B_2$, $B_6$, pantothenic acid and niacin.

### Results

No studies were located which examined the impact of multivitamin supplementation on any outcomes in LBW infants.

### Recommendations

Policy statements from organizations in developed countries describe the importance of providing multivitamin supplementation with a standard neonatal multivitamin preparation containing vitamins A, D, C, $B_1$, $B_2$, $B_6$, pantothenic acid and niacin to all LBW infants receiving human milk from birth until the infant attains a weight of 2000 g. Standard practice in many neonatal units is to provide commercially available multivitamin preparations to all LBW infants receiving unfortified human milk until 6 months chronological age. It was not possible to provide additional recommendations due to insufficient evidence.

## MULTICOMPONENT FORTIFICATION

Multicomponent fortifiers commonly contain protein, fat, carbohydrate, calcium, phosphorus, iron, zinc, vitamins A, D, E, K, and riboflavin. The constituents of commonly used fortifiers are described in Box 1.3.3.

### Results

#### Effect on mortality

Two RCTs were located which reported the impact of multicomponent supplementation of human milk on mortality rates, although the studies were not designed to examine the effect on mortality (see summary Table 2.2.7) (*17*, *168*). Lucas et al randomized 275 UK preterm infants (birth weight <1850 g, gestational age range 23–36 weeks) to receive either human milk with added standard human milk fortifier or human milk with only added vitamins, phosphate and sodium (*17*). These interventions were provided from the time that full enteral feeds were tolerated until the infant attained a weight of 2000 g. This study reported no significant impact on mortality rate (RR 0.78, 95%CI 0.30 to 2.04). Pettifor et al randomized 59 South African pre-term infants <1500 g at birth to receive maternal milk supplemented with a multicomponent fortifier or unsupplemented maternal milk from the time that enteral feeds were tolerated until hospital discharge (*168*). There were seven deaths among the study infants, all of them in the group randomized to receive the fortifier. A recently updated meta-analysis (*233*) of these two studies showed that the combined estimate of RR of death was not significantly different from 1 (RR 1.48, 95%CI 0.66 to 3.34). However, the confidence limits were wide and the RR was above 1, thus a trend towards an increased mortality risk from multicomponent fortifier cannot be discounted.

#### Effect on serious morbidity

A meta-analysis of five RCTs (*17*, *168*, *234–236*) (see summary Table 2.2.8.) showed no significant difference in the risk of necrotising enterocolitis between the multicomponent-fortifier supplemented and control groups (pooled RR 1.33, 95%CI 0.69 to 2.54) (*233*). However, confidence limits were wide and the RR was above 1, thus a trend towards an increased morbidity risk from multicomponent fortifier cannot be discounted. In addition, the large study by Lucas et al reported an increase in clinical infection (suspected or proven) in the fortified group (43% compared with 31%, P = 0.04)

(*17*). There was also a non-significant increase in the risk of necrotising enterocolitis (5.8% compared with 2.2%, P = 0.12).

### Effect on neurodevelopment

Only one RCT was located which examined the impact of multicomponent supplementation of human milk on neurodevelopmental outcomes (see summary Table 2.2.9.) (*17*). In this study no significant differences in neurodevelopment were detected at 9 or 18 months in the fortified compared to the unfortified group, though some advantages were reported in a subgroup of male infants.

### Effect on malnutrition

Ten clinical trials were located which examined the impacts of multicomponent supplementation on short-term growth (*17*, *168*, *234*, *237–243*). All trials were from developed countries and are summarized in Table 2.2.10. The two largest studies (*17*, *168*) did not find a statistically significant increase in weight gain in the fortification group. Nevertheless, the meta-analysis showed greater weight gains in infants receiving multicomponent fortifier compared to the controls (WMD 2.3 g/kg/day, 95%CI 1.7 to 2.9). Similarly, the meta-analysis reported significantly greater length gains (WMD 0.12 cm/week, 95%CI 0.07 to 0.18) and head growth (WMD 0.12 cm/week, 95%CI 0.07 to 0.16) in the fortifier group. Two studies evaluated long-term growth at 12 and 18 months of age (*17*, *241*); both found no differences in weight, length and head circumference between the study groups.

### Effect on bone mineralization

Two RCTs were located which examined the role of calcium and phosphorus supplementation as a part of multicomponent fortifier in improving bone mineralization. Modanlou et al randomized 18 US infants (*243*) and Pettifor et al randomized 59 South African infants (*168*) who weighed 1000–1600 g at birth. Both trials provided infants with calcium (2.0 mmol/kg/day) and phosphorus (0.5 mmol/kg/day) from the time when full enteral feeds were tolerated (mean age 14 days) until hospital discharge. Both studies reported that infants receiving fortification had significantly better bone mineralization than those receiving unsupplemented milk at hospital discharge. A meta-analysis of these two trials also demonstrated a significant improvement by hospital discharge (WMD 8.3mg/cm, 95%CI 3.8 to 12.8mg/cm) (*233*). However, no significant differences in bone mineralization between the intervention and the control groups were detected at 3 months by Pettifor et al and no longer-term follow-up has been reported.

## Conclusions and implications

In infants of <32 weeks gestation, there is evidence that use of multicomponent fortifier leads to short-term increase in weight gain, linear growth, head growth and bone mineralization. There are insufficient data to evaluate long-term neurodevelopmental and growth outcomes, although there appears to be no effect on growth beyond one year of age. Use of multi-component fortifiers does not appear to be associated with increased risk of mortality or necrotizing enterocolitis, although the small number of infants and the large amount of missing data in the studies reduces confidence in this conclusion. Also, in the largest trial undertaken there was a significant increase in the incidence of infection among infants receiving the fortifier. There are no data examining the efficacy of multicomponent fortifier in infants of 32–36 weeks gestation or in term LBW infants.

Almost all the studies are from developed countries. A higher prevalence of infections, greater potential for contamination, and high fortifier costs are additional issues to consider when deciding use of multicomponent fortifiers in developing countries

## Recommendations

Policy statements from developed countries describe the importance of giving supplements with a standard multicomponent fortifier from birth to growing pre-term infants weighing <1500 g at birth who receive human milk until a weight of 1800–2000 g has been reached (43, 45). Standard practice in many

neonatal units in infants with birth weights <1500 g is to add a multicomponent fortifier to human milk until the infant reaches 1800–2000 g.

The findings of this review raise doubts on the routine use of multicomponent fortifiers, particularly in developing countries. The benefits appear to be only short-term increases in growth, the safety is uncertain, and could be of more concern in developing countries with a greater risk of contamination. Further research in developing countries is needed to examine the role of multicomponent fortifiers. Meanwhile, their use should be restricted to infants <32 weeks gestation or <1500 g birth weight who fail to gain weight despite adequate breastmilk feeding.

**SUMMARY TABLE 2.2.7**
**Effect of multicomponent fortification of human milk on mortality in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Lucas et al (*17*) RCT (LII) | Birth weight <1850 g | 80% | 20% | None | Infants who received maternal milk supplemented with multicomponent fortifier (n=137) *compared with* infants who received maternal milk supplemented with phosphate alone (n=138) | Mortality until discharge | RR 0.78 (0.30, 2.04) |
| Pettifor et al (*168*) RCT (LII) | Birth weight 1000–1500 g, enteral intake at least 45 ml/kg/day | 100% | None | None | Infants who received maternal milk supplemented with multicomponent fortifier (n=53) *compared with* infants who received unsupplemented maternal milk (n=47) | Mortality during first 3 months of life | Adjusted[b] RR 13.3 (0.78, 227.4) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

[b] Adjusted for birth weight and gestational age.

**SUMMARY TABLE 2.2.8**
**Effect of multicomponent fortification of human milk on necrotising enterocolitis in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Lucas et al (*17*) RCT (LII) | Birth weight <1850 g | 80% | 20% | None | Infants who received maternal milk supplemented with multicomponent fortifier (n=137) *compared with* infants who received maternal milk supplemented with phosphate alone (n=138) | Necrotising enterocolitis | RR 2.69 (0.73, 9.91) |
| Pettifor et al (*168*) RCT (LII) | Birth weight 1000–1500 g, enteral intake at least 45 ml/kg/day | 100% | None | None | Infants who received maternal milk supplemented with multicomponent fortifier (n=53) *compared with* infants who received unsupplemented maternal milk (n=47) | Necrotising enterocolitis | Adjusted[b] RR 2.66 (0.29, 24.7) |
| Kashyap et al (*234*) RCT (LII) | Birth weight 900–1750 g | 63% | 37% | None | Infants who received maternal milk supplemented with multicomponent fortifier (n=30) *compared with* infants who received unsupplemented maternal milk (n=36) | Necrotising enterocolitis | RR 0.53 (0.18, 1.56) |
| Zuckerman et al (*235*) RCT (LII) | Birth weight <1200 g | 100% | None | None | Infants who received maternal milk supplemented with multicomponent fortifier (n=29) *compared with* infants who received unsupplemented maternal milk (n=24) | Necrotising enterocolitis | RR 0.83 (0.05, 12.6) |
| Faerk et al (*236*) RCT (LII) | Gestational age <32 weeks | 100% | None | None | Infants who received maternal milk supplemented with multicomponent fortifier (n=36) *compared with* infants who received maternal milk supplemented with phosphorus (n=40) | Necrotising enterocolitis | RR 1.11 (0.07, 17.12) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.
[b] Adjusted for birth weight and gestational age.

## SUMMARY TABLE 2.2.9
### Effect of multicomponent fortification of human milk on neurodevelopment in LBW infants

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| | | | | | | | Difference in mean scores |
| Lucas et al (*17*) RCT (LII) | Birth weight <1850 g | 80% | 20% | None | Infants who received maternal milk supplemented with multi-component fortifier (n=137) *compared with* infants who received maternal milk supplemented with phosphate alone (n=138) | Overall developmental quotient at 9 months | 0.5 (-2.7 to 3.7) |
| | | | | | | Bayley's mental development index score at 18 months | 2.2 (-3.4 to 7.8) |
| | | | | | | Bayley's psychomotor development index score at 18 months | 2.4 (-1.9 to 6.7) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500g to have a gestation of 37 weeks or more.

## SUMMARY TABLE 2.2.10
### Key studies which examine the effect of multicomponent fortification of human milk on growth outcomes in LBW infants

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| | | | | | | | Weighted mean difference |
| Lucas et al (*17*) RCT (LII) | Birth weight <1850 g | 80% | 20% | None | Maternal milk supplemented with multicomponent fortifier (n=137) *compared with* maternal milk supplemented with phosphate alone (n=138) | Weight gain (g/kg/day) | 0.60 (-0.38, 1.58) |
| Pettifor et al (*168*) RCT (LII) | Birth weight 1000–1500 g | 100% | None | None | Maternal milk supplemented with multicomponent fortifier (n=53) *compared with* unsupplemented maternal milk (n=47) | Weight gain (g/kg/day) | -0.10[b] (-3.15, 2.95) |
| Kashyap et al (*234*) RCT (LII) | Birth weight 900–1750 g | 63% | 37% | None | Maternal milk supplemented with multicomponent fortifier (n=30) *compared with* unsupplemented maternal milk (n=36) | Weight gain (g/kg/day) | 4.02 (2.30, 5.74) |
| Carey et al (*237*) RCT (LII) | Birth weight <1500 g | 100% | None | None | Maternal milk supplemented with multicomponent fortifier (n=6) *compared with* unsupplemented maternal milk (n=6) | Weight gain (g/kg/day) | 5.7 (2.66, 8.74) |

*continued*

**SUMMARY TABLE 2.2.10 *continued***

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| | | | | | | | Weighted mean difference |
| Greer et al (*238*) RCT (LII) | Infants <32 weeks or <1600g | 90% | 10% | None | Maternal milk supplemented with multicomponent fortifier (n=10) *compared with* unsupplemented maternal milk (n=10) | Weight gain (g/kg/day) | 3.86 (2.50, 5.22) |
| Nicholl et al (*239*) RCT (LII) | Birth weight <1500 g | 100% | None | None | Maternal (or donor) milk supplemented with multi-component fortifier (n=13) *compared with* unsupplemented maternal or donor milk (n=10) | Weight gain (g/kg/day) | 1.90 (-2.45, 6.25) |
| Pollberger et al (*240*) RCT (LII) | AGA preterm infants <1500 g | 100% | None | None | Maternal (or donor) milk supplemented with human milk protein and fat (n=7) *compared with* unsupplemented human milk (n=7) | Weight gain (g/kg/day) | 5.10 (1.95, 8.25) |
| Wauben et al (*241*) RCT (LII) | Preterm infants <1800 g, aged > 1 week | 85% | 15% | None | Maternal milk supplemented with multicomponent fortifier (n=12) *compared with* unsupplemented maternal milk (n=13) | Weight gain (g/kg/day) | 2.40 (0.99, 3.81) |
| Gross et al (*242*) RCT (LII) | Birth weight <1600 g | 100% | None | None | Maternal milk supplemented with multicomponent fortifier (n=8) *compared with* unsupplemented maternal milk (n=9) | Weight gain (g/day) | 10.30 (6.68, 13.92) |
| Modanlou et al (*243*) RCT (LII) | Birth weight 1000–1500 g | 100% | None | None | Maternal milk supplemented with multicomponent fortifier (n=8) *compared with* unsupplemented maternal milk (n=10) | Weight gain (g/day) | 4.20 (0.72, 7.68) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

[b] Adjusted for birth weight and gestational age

## 2.3 Breastmilk substitutes

Breastmilk substitutes are used if human milk feeding of a LBW infant is not possible. There are many different commercial formulations and the nutrient composition of each breastmilk substitute is slightly different, reflecting the uncertainty about a pre-term infant's need for nutrients, specifically the protein-energy ratio, fat blend, and amounts of calcium and phosphorus. Breastmilk substitutes also do not contain any of the biologically active immune substances, or hormones or growth factors that are found in human milk.

The effect of different breastmilk substitutes on clinical outcomes is important to consider when choosing which breastmilk substitutes to use for LBW infants who cannot be fed human milk. The following are reviewed below:

- Locally prepared animal milk;
- Pre-term versus standard infant formula during the first few days of life;
- Nutrient-enriched formula versus standard formula after discharge from the hospital.

### LOCALLY PREPARED ANIMAL MILK

#### Results

No studies examining the impact on clinical outcomes were located.

#### Recommendations

No policy statements on the use of local preparations of animal milk were located from international or national organizations in developed or developing countries. Standard practice in neonatal units of developing countries is to provide artificial infant formula when human milk is not available. If artificial infant formula is not available, then pasteurized (heat treated/boiled to 62 °C) and diluted animal milk (100 ml milk + 50 ml water) has been used with sugar (10 g to 100 ml milk + 50 ml water) and nutritional supplements (iron, zinc, copper, manganese and iodine, vitamins A, D, E, K, C, $B_1$, $B_2$, $B_6$, $B_{12}$, niacin, folic acid, pantothenic acid and biotin) added, as available. It was not possible to provide additional recommendations due to insufficient evidence.

### PRE-TERM VERSUS STANDARD INFANT FORMULA DURING THE FIRST FEW DAYS OF LIFE

#### Results

##### Effects on mortality and morbidity

No studies, which examined the impact of pre-term compared with standard infant formula on mortality rates or serious clinical disease in LBW infants, were located.

##### Effect on neurodevelopment

One large RCT was located which examined the impact of term and pre-term formula on neurodevelopmental outcomes in pre-term infants (*244*, *245*) (see summary Table 2.3.1). In this multicentre study, Lucas et al randomized 424 UK pre-term infants (whose mothers did not intend to breastfeed) to receive pre-term or standard infant formula from birth until a weight of 2000 g was attained. Lucas et al reported significant advantages in psychomotor developmental scores at 18 months in infants fed pre-term formula (*244*). This effect was greater in two subgroups – in infants who were small for gestation and in males (see summary Table 2.3.1). In a follow-up of participants of the same trial at 8 years of age, Lucas et al reported no significant benefit in overall IQ in the pre-term formula-fed infants (*245*). However, there was a significant advantage in verbal intelligence quotient among boys fed pre-term infant formula. In a post-hoc analysis, the incidence of cerebral palsy was significantly lower in the pre-term compared to the standard infant-formula-fed group (see summary Table 2.3.1).

##### Effect on malnutrition

Only one study was located which examined the long-term impacts of pre-term and standard infant formula on growth (*182*). It reported significantly higher weight gain at hospital discharge in infants fed pre-term formula but no significant differences in weight, height or head circumference at 18 months and at 7½–8 years in infants who had been fed pre-term or standard infant formula (see summary Table 2.3.2).

### Effect on bone mineralization

Morley and Lucas conducted a large RCT which examined the effect of pre-term compared with standard infant formula on bone mineralization (*182*). No significant differences in bone mineral calcium, bone mineral density and osteocalcin were measured at follow-up of 244 infants at age 8–12 years (*186*).

### Effect on blood pressure, insulin resistance and lipid profile during adolescence

Data from follow-up at age 13–16 years of participants of the trials conducted by Lucas et al have recently been published (*24*, *25*, *183*). There were no significant differences between infants fed pre-term formula or a standard infant formula in mean arterial blood pressure (–1.5 mm Hg, 95%CI –3.9 to 2.0, P=0.51), fasting 32–33 split proinsulin (–23.1%, –48% to 1.8%, P=0.07), or LDL/HDL ratio (–0.3, 95%CI –0.7 to 0.3, P=0.07).

## Conclusions and implications

There is some evidence that pre-term infant formula is better than standard infant formula for pre-term infants <1500 g at birth. Infants (<1500 g) fed pre-term infant formula had higher psychomotor developmental scores than those fed standard infant formula up to 18 months of age. Although there was no overall effect observed in these children at 7½–8 years of age, there was some effect on verbal IQ scores in a subgroup. In infants <1500 g, pre-term compared to standard infant formula also improved growth during the neonatal period, but there is no evidence that this benefit was sustained during later infancy and childhood. No other longer-term benefits (e.g. related to blood pressure, serum lipid profile or pro-insulin levels) have been reported.

No studies from developing countries were located. In case breastmilk feeding is not possible, it may be preferable to use pre-term infant formula for pre-term infants <1500 g at birth. LBW infants with birth weight >1500 g are not likely to benefit from the use of pre-term infant formula and can be given standard infant formula in case breastmilk feeding is not possible.

## Recommendations

Policy statements from international and national organizations confirm the importance of providing mother's own breastmilk for the LBW infant. For the nonhuman-milk-fed infant, pre-term formula is recommended until the infant attains a body weight of 2000 g, followed by iron-fortified standard infant formula until the infant is 12 months of age. The findings from this review support these recommendations.

**SUMMARY TABLE 2.3.1**
**Effect on neurodevelopment of pre-term formula compared with standard infant formula from birth until LBW infants attained a weight of 2000 g**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| | | | | | | | Difference in mean score |
| Lucas et al (*244*) RCT (LII) | Birth weight <1850 g | 80% | 20% | None | Infants of mothers choosing not to provide breastmilk allocated to receive pre-term formula (n=81) *compared with* infants who were allocated to receive a standard infant formula (n=79) | Bayley mental development index score at 18 months | 6.0 (-0.4, 12.6) |
| | | | | | | Psychomotor development index score at 18 months | 14.7 (8.7, 20.7) |
| Lucas et al (*245*) RCT (LII) | Birth weight <1850 g | 80% | 20% | None | Infants of mothers choosing not to provide breastmilk allocated to receive pre-term formula (n=67) *compared with* infants who were allocated to receive a standard infant formula (n=66) | Verbal IQ at 7.5–8 years with abbreviated Weschler intelligence scale for children | All children: 4.8 (-0.6 to 10.2)<br>Boys: 12.2 (3.7 to 20.6)<br>Girls: -2.2 (-9.0 to 4.6) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**SUMMARY TABLE 2.3.2**
**Effect of pre-term formula compared with standard infant formula on growth outcomes in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| | | | | | | | Mean difference |
| Morley and Lucas (*182*) RCT (LII) | Birth weight <1850 g | 80% | 20% | None | Infants of mothers choosing not to provide breast milk allocated to receive pre-term formula (n=67) *compared with* infants who were allocated to receive a standard infant formula (n=68) | Weight gain in neonatal period (g/kg/day) | 3.2 (1.8, 4.6) |
| | | | | | | Length gain in neonatal period (mm/d) | 0.2 (-0.07, 0.47) |
| | | | | | | Weight at 18 months post term (kg) | 0.2 (-0.32, 0.72) |
| | | | | | | Length at 18 months post term (cm) | 1.2 (-0.28, 2.68) |
| | | | | | | Weight at 7.5–8 years post term (kg) | 0.3 (-1.0, 1.6) |
| | | | | | | Length at 7.5–8 years post term (cm) | 1.3 (-0.71, 3.31) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to have <32 wk gestation, those weighing 1501–2000 g to have 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## NUTRIENT-ENRICHED FORMULA VERSUS STANDARD FORMULA

### Results

#### Effect on mortality and morbidity

No studies were located which examined the impact of infant formula on mortality rates or serious clinical disease in LBW infants.

#### Effect on neurodevelopment

Two RCTs was located which examined the impact of nutrient-enriched formula on neurodevelopmental outcomes, compared with standard infant formula (*160*, *246*). Lucas et al randomized 284 UK pre-term infants (whose mothers did not intend to breastfeed) to receive nutrient-enriched or standard infant formula from hospital discharge until 9 months of chronological age (*160*). There was a 2.8-point advantage in Bayley's psychomotor index subscale in infants fed nutrient-enriched formula when they had reached 18 months of chronological age, but this difference was not statistically significant. There was no difference in mental development scores in the two study groups (see summary Table 2.3.3). Cooke et al randomized 125 US pre-term infants (whose mothers did not intend to breastfeed) to receive nutrient-enriched or standard infant formula from hospital discharge until 6 months of chronological age (*246*). He also did not find a statistically significant difference in Bayley's mental development index or psychomotor development index at 18 months post-term. Meta-analysis of data from Cooke et al and Lucas et al did not find a statistically significant difference in either the mental development index (WMD 0.23, 95%CI –2.99 to 3.45) or psychomotor development index (WMD 0.56, 95%CI –1.95 to 3.07)) (*247*). No longer-term follow-up for neurodevelopment has been reported.

#### Effect on malnutrition

Six studies were located which examined the impacts of nutrient-enriched formula on growth outcomes (*160*, *161*, *246*, *248–250*). Studies examining long-term growth impacts are summarized in Table 2.3.4. Litmanowitz (*249*), de Curtis et al (*250*) and Cooke et al (*246*) did not find any statistically significant short-term growth gains in their nutrient-enriched formula groups. However, Carver et al (*248*), Lucas et al (*160*) and Cooke et al (*246*) reported variable long-term (up to 18 months of age) linear and weight gains in their nutrient-enriched formula groups. Meta-analysis of data from Cooke et al and Lucas et al found a statistically significant effect of calorie and protein-enriched formula milk on crown-heel length at 18 months post-term (WMD 9.8, 95%CI 2.9, 16.6 mm), but not on weight (WMD 24.0, 95%CI –4.1 to 51.9 g), or head circumference (WMD 0.3, 95%CI –3.6 to 4.3 mm) (*247*). In the study of term SGA infants by Fewtrell et al, infants fed nutrient-enriched formula had significantly greater gains in length and head circumference at 9 and 18 months chronological age (*161*). He also reported that the dietary effects were independent of the pattern of growth retardation. No studies were located which reported impacts on standard deviation scores or malnutrition rates.

### Conclusions and implications

There is weak evidence that nutrient-enriched formula results in higher weight and length gains over standard infant formula in pre-term infants. There is no evidence of benefit on any other outcomes. There is some evidence that term SGA infants fed nutrient-enriched formula had improved ponderal, linear and head growth. The longer-term implications of faster growth in these infants on later blood pressure, insulin resistance and lipid profile needs to be carefully examined before making any recommendations for use of nutrient-enriched formula.

No studies from developing countries were located. Considering the weak evidence of benefits and substantially higher costs of nutrient-enriched formula, its routine use cannot be justified in developing country settings.

### Recommendations

Policy statements from international and national organizations confirm the importance of providing mother's own breastmilk

for LBW infants. For the nonhuman-milk-fed infant, pre-term formula is recommended until the infant attains a body weight of 2000 g, followed by iron-fortified standard infant formula until the infant is 12 months of age. It was not possible to provide additional recommendations due to insufficient evidence.

**SUMMARY TABLE 2.3.3**
**Effect of nutrient-enriched formula compared with standard infant formula on neurodevelopment in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| | | | | | | | Difference in mean score |
| Lucas et al (*160*) RCT (LII) | Birth weight <1750 g | 70% | 30% | None | Infants of mothers choosing not to provide breastmilk allocated to receive nutrient-enriched formula (n=91) *compared with* infants who were allocated to receive for 9mo a standard infant formula (n=93) after discharge from the hospital | Bayley mental development index score at 18 months | 0.9 (-3.3, 5.0) |
| | | | | | | Psychomotor development index score at 18 months | 2.8 (-1.3, 6.8) |
| Cooke et al (*246*) RCT (LII) | Birth weight <1750 g | 80% | 20% | None | Infants of mothers choosing not to provide breastmilk allocated to receive nutrient-enriched formula (n=49) compared with infants who were allocated to receive for 6mo a standard infant formula (n=54) after discharge from the hospital | Bayley mental development index score at 18 months | -1.0 (-6.4, 4.4) |
| | | | | | | Psychomotor development index score at 18 months | -1.0 (-4.3, 2.3) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**SUMMARY TABLE 2.3.4**
**Effect of nutrient-enriched post-discharge formula compared with standard infant formula on growth outcomes in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| | | | | | | | Difference in means |
| Lucas et al (*160*) RCT (LII) | Birth weight <1750 g | 70% | 30% | None | Infants of mothers choosing not to provide breastmilk allocated to receive post-discharge formula (n=116) *compared with* infants who were allocated to receive a standard infant formula (n=113) after discharge from the hospital | Weight (kg) at 9mo<br>Length (cm) at 9mo<br>Head circumference (cm) at 9 mo<br>Weight (kg) at 18mo<br>Length (cm) at 18 mo<br>Head circumference (cm) at 18 mo | 0.37 (0.084, 0.66)<br>1.10 (0.31, 1.89)<br>0.001 (-0.45, 0.46)<br>0.094 (-0.26, 0.44)<br>0.82 (-0.039, 1.69)<br>-0.38 (-0.90, 0.13) |
| Carver et al (*248*) RCT (LII) | Pre-term infants <1800 g | 100% | None | None | Infants allocated to receive nutrient-enriched formula (n=27) *compared with* infants allocated to receive a standard infant formula (n=27) from just before hospital discharge to 12 mo age | Weight (kg) at 12 mo<br>Length (cm) at 12 mo<br>Head circumference (cm) at 12 mo | 0.51 (-0.26, 1.28)<br>1.1 (-0.87, 3.1)<br>0.3 (-0.87, 3.1) |
| Cooke et al (*246*) RCT (LII) | Birth weight <1750 g | 80% | 20% | None | Infants of mothers choosing not to provide breastmilk allocated to receive nutrient-enriched formula (n=49) *compared with* infants allocated to receive a standard infant formula (n=54) after discharge from the hospital for 6mo | Weight (kg) at 18 mo<br>Length (cm) at 18 mo<br>Head circumference (cm) at 18 mo | 0.05 (0.003, 0.097)<br>1.1 ( -0.02, 2.2)<br>0.5 (-0.1, 1.1) |
| Fewtrell et al (*161*) RCT (LII) | Healthy term infants with birth weights below the 10th centile | None | None | 100% | Infants allocated to receive nutrient-enriched formula (n=152) *compared with* infants who were allocated to receive a standard infant formula (n=147) after discharge from the hospital | *Enrolment to 9 mo*<br>Weight (kg) gain<br>Length (cm) gain<br>Head circumference (cm) gain<br>*Enrolment to 18 mo*<br>Weight (kg) gain<br>Length (cm) gain<br>Head circumference (cm) gain | <br>0.22 (-0.01, 0.45)<br>1.1 (0.38, 1.8)<br>0.5 (0.1, 0.9)<br><br>0.25 (-0.032, 0.54)<br>1.0 (0.25, 1.82)<br>0.63 (0.2, 1.1) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to have <32 wk gestation, those weighing 1501–2000 g to have 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

# 3. FEEDING METHODS

Enteral feeding is defined as the administration of any feed into the gastrointestinal tract and includes intragastric feeding, feeding by cup, bottle, spoon or paladai, and breastfeeding. In this section we review the types of enteral feeding options available. Intravenous fluids and total parenteral nutrition are not discussed. A pre-term infant's progression to breastfeeding must pass through a number of stages before the infant begins to swallow, coordinate and then learn proper attachment and sucking. Different forms of enteral and oral feeding have been used during this transition.

## 3.1 Oral feeding

Oral feeding methods discussed below include administration of any feed directly into the oral cavity by a method other than breastfeeding: cup, paladai, spoon, syringe, direct expression and bottle feeding. In this section, studies that compared these different oral feeding methods are compared. The studies utilized small medicine cups, standard infant feeding bottles, standard 10 or 20 ml syringes, or a paladai shaped like a small cup with an open spout on one side.

### Results

#### Effects on mortality, serious morbidity, neurodevelopment or malnutrition

No studies were located which compared the effects of different oral feeding methods (cup, bottle, paladai, spoon, direct expression) on mortality, severe morbidity, neurodevelopment, growth or malnutrition rates in LBW infants.

#### Effects on other important outcomes

Breastfeeding rates, at the time of discharge from hospital or at subsequent follow-ups, and physiological parameters were the outcomes reported in studies that compared different feeding methods. Most studies compared cup feeding with bottle feeding. One Indian study compared cup, bottle and paladai feeding (*251*). No studies were identified that compared spoon feeding or direct expression of breastmilk into the infant's mouth with other oral feeding methods.

Only one RCT (Level II evidence) from Australia, which compared the effect of cup feeding with bottle feeding on *breastfeeding patterns* (see Table 3.1.1) (*252*), reported that infants randomized to cup feeds were more likely to be fully breastfed (with no other types of milk or solids other than breastmilk) on discharge home (odds ratio [OR] 1.73, 95%CI 1.04 to 2.88), and had a longer length of stay in hospital (hazard ratio [HR] 0.71, 95%CI 0.55 to 0.92). The prevalence of any breastfeeding was apparently higher in the cup-feeding group compared with the bottle-feeding group at 3 and 6 months, but the differences were not statistically significant. Another small RCT showed no differences in the proportion of infants receiving any breastfeeding at discharge between cup-fed and bottle-fed preterm infants, but there was a higher prevalence of breastfeeding at 3 months among those who were breastfeeding at the first follow-up visit (*253*). This study did not report the effect on exclusive or full breastfeeding rates.

Small observational studies (LIII-3 evidence) from the UK, US and India have reported mixed effects of cup, bottle and paladai feeding on breastfeeding rates, milk volume intake, feeding duration, and feeding difficulties at the time of hospital discharge in LBW infants (32–42 weeks gestation) (*251*, *254–256*). These studies all had problems with observer and selection biases, insufficient discussion of confounding factors, and lack of follow-up after hospital discharge.

The impact of oral feeding on *physiological parameters* in LBW infants has been reported in four studies (*251*, *253*, *256*, *257*). Rocha et al reported no significant differences between cup-fed and bottle-fed infants with regard to the time spent in feeding, feeding problems, weight gain, or breastfeeding prevalence at discharge or at the 3-month follow-up (*253*). A possible beneficial effect of cup feeding was

**SUMMARY TABLE 3.1.1**
**Effects of cup feeding compared with bottle feeding on breastfeeding patterns in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Collins et al (*252*) RCT (LII) | Gestational age <34 weeks, no previous cup or bottle feeding, mother intended to breastfeed | 62% | 38% | None | After breastfeeding or when mother unable to be present, infants fed by cup (n = 151) *compared with* infants fed by bottle (n = 152) | Proportion of infants fully breastfed at hospital discharge | OR 1.73 [1.04, 2.38] |
| | | | | | | Proportion of infants receiving any BF at hospital discharge | OR 1.37 [0.78, 2.38] |
| | | | | | | Proportion of infants receiving any BF at 3 months after discharge | OR 1.31 [0.77, 2.23] |
| | | | | | | Proportion of infants receiving any BF at 6 months after discharge | OR 1.44 [0.81, 2.57] |
| Rocha et al (*253*) (RCT LII) | Gestational age 32–36 weeks | None | 100% | None | Infants randomized to cup feeding (n=44) *compared with* those randomized to bottle feeding (n=34) | Proportion of infants receiving any breast-feeding at discharge | RR 1.03 (0.83, 1.28) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

a lower incidence of desaturation episodes (13.6% versus 35.3%, CF vs. BF, P = .024). Another US study used a randomized cross-over trial in pre-term infants (LII evidence) (*257*) to receive either 1 cup feed followed by 1 bottle feed, or 1 bottle feed followed by 1 cup feed when they reached 34 weeks corrected gestational age (there was a minimum of 1 intragastric feeding between the two oral feeding sessions). Lower mean heart rate and oxygen saturations in bottle-fed compared to cup-fed infants were reported in this study, but all other physiological parameters were not significantly different. Finally two small observational studies, which examined the impacts of different oral feeding methods in LBW infants (LIII-3 evidence) (Malhotra et al (*251*): cup, bottle and paladai; and Howard et al (*256*): cup and bottle), reported small deteriorations in physiological parameters in bottle-fed infants.

## Conclusions and implications

None of the available studies examined the effects of different oral feeding methods on mortality, morbidity, neurodevelopment or malnutrition. The findings are largely based on three RCTs and small observational studies which examined the effect of cup feeding compared to bottle feeding on breastfeeding rates at the time of hospital discharge in pre-term infants. Some studies, including the larger RCT, reported modest benefits of cup feeding on EBF rates at discharge from hospital. Evidence was insufficient to allow conclusive statements on the safety of the methods. Overall, the above findings suggest that cup feeding has some benefits over bottle feeding with regard to achieving full breastfeeding and physiological stability in pre-term infants.

Most of the studies comparing cup feeding with bottle feeding were conducted in developed countries. Avoidance of bottle feeding

is likely to have greater benefits in developing countries because of the higher risk of contamination of bottle feeds in these settings.

### Recommendations

Cup feeding is recommended as a feeding method for sick and LBW infants by WHO and UNICEF. Bottle feeding is not recommended. Standard practice in many neonatal units is to progress from cup feeding to breastfeeding, or bottle feeding to breastfeeding, or paladai feeding to breastfeeding. The findings from this review support these recommendations.

## 3.2 Intragastric feeding

Intragastric feeding involves the administration of milk feeds through a thin small plastic tube that passes through the nose or mouth directly into the stomach. Intragastric feeding is commonly used in developed countries when infants are too developmentally immature to swallow or coordinate feeds or when more mature LBW infants have associated pathology which might limit oral feeding. This is generally before 32 weeks gestation but can extend to 34–35 weeks gestation depending on the developmental maturity of the infant. Considerable skill is required to insert intragastric tubes in small infants. Nasogastric rather than orogastric tubes appear to be more commonly used in pre-term babies with ≥32 weeks gestation as they are more easily fixed in place. However, nasogastric tubes partially occlude the nasal passages and may impair respiratory function. Orogastric tubes may be better for very premature infants who usually have smaller nostrils. Intragastric feeding is usually provided as either a bolus feeding session (where a calculated amount of milk is poured into the tube over a period of 10–30 minutes every 1–3 hours, depending on the infant's weight and gestational age) or a continuous feed (where the tube is attached to a syringe pump, from where the milk runs through the tube into the infant's stomach continuously for 18–24 hours).

The following issues are reviewed below:

- Use of nasogastric versus orogastric tubes;
- Bolus versus continuous intragastric feeding.

### USE OF NASOGASTRIC VERSUS OROGASTRIC TUBES

#### Results

##### Effects on mortality, serious morbidity, neurodevelopment and malnutrition

No studies were located which examined the effects of intragastric tube type on mortality, severe morbidity, neurodevelopment, growth or malnutrition in LBW infants.

##### Effects on other important outcomes

In one RCT (LII evidence), which examined the effects of intragastric tubes in pre-term infants on *gastrointestinal tolerance* (see summary Table 3.2.1), 70 Swedish VLBW infants weighing <1200 g (<29 weeks gestation) were randomized to receive continuous nasogastric, intermittent orogastric or intermittent nasogastric tube feeds (*258*). The primary analysis was the comparison between continuous and intermittent/bolus tube feeding. A secondary objective was to assess the impact of orogastric versus nasogastric tube feeding on gastrointestinal tolerance and infant behaviour; however, no sample size calculations were performed and the study numbers were small (n=46). No significant differences between orogastric and nasogastric tube feeding on the time to achieve full enteral feeding, total energy intake or total protein intake were reported.

One RCT (LII evidence) (*258*) and three descriptive studies (LIV evidence) examined the effects of intragastric tubes in pre-term infants on *physiological parameters* (*259–261*). The study of Dsilna et al, described above, examined the impacts on physiological parameters as a post-hoc analysis and reported no significant impacts on respiratory distress syndrome, mechanical ventilation or need for supplemental oxygen (see summary Table 3.2.2). Greenspan et al examined lung function in a small US study of 39 healthy

infants; 24 of them had an orogastric or nasogastric tube *in situ* (14 weighed <2000 g and 10 weighed >2000 g at birth); 15 had no intragastric tube (*260*). No infant showed clinical compromise after nasogastric and orogastric tube placement, but infants <2000 g at birth had signs of subclinical pulmonary compromise (diminished minute ventilation, low respiratory rate, increased pulmonary resistance, resistive work of breathing, and peak transpulmonary pressure change) with nasogastric compared to orogastric tube placement. Daga et al examined oxygen saturations during the passage of orogastric and nasogastric tubes and 10–30 minutes after feeds in 10 stable Indian newborns (4 term infants with birth weights >2500 g and 6 pre-term infants of 31–35 weeks gestation) (*261*). Mean oxygen saturations were significantly lower during the passage of nasogastric compared to orogastric tubes and persisted for up to 30 minutes after feeding. In a small UK study, nasal resistance and total airway resistance were reported to increase after nasal tubes were inserted into the nostrils of 20 LBW infants <32 weeks gestation (*259*). The infants were also assessed one month after removal of the nasogastric (n=20) or orogastric tube (n=20); no differences were detected in nasal resistance and total airway resistance between the two groups. No studies provided data about potential confounding factors or selection and observer biases.

## Conclusions and implications

Overall, data on the effect of nasogastric compared with orogastric feeding tubes on clinical outcomes are limited. There is some evidence that physiological parameters may be worse with nasogastric tube placement in very preterm infants.

## Recommendations

No consensus statements or expert committee reports were located which recommended orogastric or nasogastric tubes in LBW infants. Both nasogastric and orogastric feeding tubes are used in neonatal intensive care units. Some units use orogastric rather than nasogastric feeding tubes for very premature infants. It was not possible to provide additional recommendations due to insufficient evidence.

**SUMMARY TABLE 3.2.1**
**Effects of nasogastric compared with orogastric feeding on feeding patterns in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Dsilna et al (*258*) RCT (LII) | Birth weight <1200 g, gestation 24–29 weeks | 100% | None | None | Nasogastric tube feeding (n=22) *compared with* orogastric tube feeding (n=24) | Time to achieve full enteral feeding (days) | WMD -2.7 [-12.31, 6.92] |
| | | | | | | Total energy intake (kcal/kg/day) | WMD 1 [-9.06, 11.06] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**Summary Table 3.2.2**
**Effects of nasogastric compared with orogastric feeding on physiological parameters in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Dsilna et al (*258*) RCT (LII) | Birth weight <1200 g, gestation 24–29 weeks | 100% | None | None | Nasogastric tube feeding (n = 22) *compared with* orogastric tube feeding (n = 24) | Respiratory distress syndrome | RR 1.09 [0.77, 1.53] |
| | | | | | | Need for mechanical ventilatory support | RR 1.31 [0.91, 1.88] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## BOLUS VERSUS CONTINUOUS INTRAGASTRIC FEEDING

### Results

#### Effects on mortality

No studies were located which examined the effects of bolus and continuous intragastric feeding on mortality in LBW infants.

#### Effects on severe morbidity – necrotising enterocolitis

A meta-analysis of all available RCTs up to the year 2003 (four US trials) (Level I evidence) indicated no significant difference in feeding infants <1500 g with bolus or continuous regimens on proven necrotising enterocolitis (Bells stage II or greater) (*262*) (see summary Table 3.2.3). In three trials there were no differences between groups in the incidence of proven necrotising enterocolitis (*263–265*) and the fourth trial showed no cases of necrotising enterocolitis in the study infants (see summary Table 3.2.3) (*266*). One additional study was published after the meta-analysis (*258*). Dsilna et al randomized 70 Swedish VLBW infants <1200 g (<29 weeks gestation) to receive continuous nasogastric or intermittent orogastric or intermittent nasogastric tube feeding (*258*) (Table 3.2.3). The primary analysis was to compare continuous and intermittent/bolus tube feeding; however, no sample size calculations were performed and the study numbers were small (n=68). Dsilna et al reported that only two infants in the continuous group and one infant in the bolus feeding group developed necrotising enterocolitis, with no significant differences between the two groups.

#### Effects on malnutrition

Meta-analyses of all available RCTs until 2003 (four US trials) (Level I evidence) indicated no significant differences in feeding infants (birth weights <1500 g) with bolus or continuous regimens on growth parameters (see summary Table 3.2.4) (*262*). Only one RCT demonstrated slower weight gain among the continuously fed infants (*264*). All other trials demonstrated no significant difference in growth (*263*, *265*, *266*). No studies examining the impacts on malnutrition and standard deviation scores were located and no studies reporting outcomes in infants >1500 g were located. Dsilna et al also reported no significant impacts on the time to regain birth weight or lower limb growth in VLBW infants (Table 3.2.4).

#### Effects on other important outcomes

Three RCTs were located which reported the impact of feeding infants <1500 g on *respiratory complications* such as apnoea, respiratory distress syndrome and the need for ventilatory support (Level II evidence) (*258*, *264*, *265*) (see summary Table 3.2.5). Schanler et al demonstrated a trend towards increased number of apnoeic episodes during the study period in infants fed by continuous feeding method (*264*). On the other hand, Silvestre et al reported that only infants in the intermittent feeding group (750–999 g weight category) had feedings withheld due to recurrent

apnoea (data not provided) (*265*), and Dsilna et al reported no differences between the two groups on the need for mechanical ventilatory or continuous positive airway pressure support (*258*).

A meta-analysis of four US trials (Level I evidence) also reported that infants took significantly longer to *reach full enteral feeds* when fed by the continuous tube feeding method compared to bolus feeding (*262*). However, a recent study by Dsilna et al reported that continuously fed VLBW infants achieved full enteral feeding significantly faster than the intermittently fed infants (adjusted hazard ratio [HR] 1.86, 95%CI 1.07 to 3.22). In a stratified analysis according to birth weight, the improvement was even more pronounced in the smallest infants, those with birth weights ≤850 g (adjusted HR 4.13, 95%CI 1.48 to 11.53).

No difference was reported in the one trial that was designed to detect outcome on the number of *days to full oral feeds* (*264*), and no difference was reported in three RCTs on rates of *feeding tolerance* (*263*, *265*, *266*). No studies reporting outcomes in infants >1500 g were located.

*Nutrient losses* from human milk during tube feeding have been determined from laboratory models. Fat and protein losses can occur and continuous feeding has been reported to result in significantly greater losses than bolus feeding (*267–269*).

## Conclusions and implications

The findings of this section are based on meta-analyses or large RCTs performed in the US or the UK in infants who weighed <1500 g at birth. Infants reached full enteral feeds sooner when fed by intermittent bolus tube feeding. There is some evidence that continuous feeding could result in loss of some nutrients that stick to the syringe pump and tube. However, the clinical risks and benefits of continuous and bolus nasogastric tube feeding of milk cannot be reliably discerned from the current available evidence because of the small sample sizes and inconsistencies in controlling the variables that affect the outcomes.

### Infants <32 weeks gestation (or birth weights <1500 g if gestation is not available)

Impacts were variable in these infants but there is some evidence that bolus feeding can reduce the time to full enteral feeding; no conclusions can be made about other advantages or disadvantages.

### Infants 32–36 weeks gestation (or birth weights 1500–2000 g if gestation is not available)

There are no data for this group of infants comparing continuous with bolus intragastric feeding.

### Term LBW infants (or birth weights >2000 g if gestation is not available)

There are no data for this group of infants comparing continuous with bolus intragastric feeding. These infants do not routinely require intragastric feeding.

All studies were conducted in developed countries. An additional issue in developing countries is that continuous feeding requires a syringe pump and frequent monitoring, which is often not possible in many maternity wards or neonatal units. On the other hand, bolus feeding requires only a gastric tube and monitoring of individual feeds which may be more feasible in these settings.

## Recommendations

No consensus statements or expert committee reports were located which examined the role of bolus or continuous feeding in LBW infants. Standard practice in many neonatal units is to use bolus feeding in infants (<1500 g at birth) with a gastric tube. The findings from this review support these recommendations.

### SUMMARY TABLE 3.2.3
### Effects of continuous feeding compared with bolus feeding on necrotising enterocolitis in LBW infants

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Premji et al (*262*) Meta-analysis of 4 RCTs (LI) | Birth weight <1500 g | 100% | None | None | Continuous feeding (n=192) *compared with* bolus feeding (n=192) | Proven necrotising enterocolitis Bell's stage II or greater | RR 0.96 [0.49, 1.90] |
| Dsilna et al (*258*) RCT (LII) | Birth weight <1200 g, gestation 24–29 weeks | 100% | None | None | Continuous feeding (n=22) *compared with* bolus feeding (n=46) | Proven necrotising enterocolitis Bell's stage II or greater | RR 4.18 [0.40, 43.7] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

### SUMMARY TABLE 3.2.4
### Effects of continuous feeding compared with bolus feeding on growth outcomes in LBW infants

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Premji et al (*262*) Meta-analysis of 4 RCTs (LI) | Birth weight <1,500 g | 100% | None | None | Continuous feeding (n=192) *compared with* bolus feeding (n=192) | Days to regain birth weight | WMD -0.6 [-1.78, 0.6] |
| | | | | | | Weight gain g/kg/day | WMD -1.1 [-2.3, 0.03] |
| Dsilna et al (*258*) RCT (LII) | Birth weight <1200 g, gestation 24-29 weeks | 100% | None | None | Continuous feeding (n=22) *compared with* bolus feeding (n=46 | Time to regain birth weight (days) | WMD -0.1 [-2.15, 1.95] |
| | | | | | | Growth rate of the lower leg, from birth to 32 weeks post-menstrual age (mm/day) | WMD 0.1 [0.04, 0.16] |
| | | | | | | Growth rate of the lower leg, from birth to 36 weeks post-menstrual age (mm/day) | WMD 0.08 [0.03, 0.13] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**SUMMARY TABLE 3.2.5**
**Effects of continuous compared with bolus feeding on respiratory complications in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Schanler et al (*264*) RCT (LII) | Birth weight <1500 g | 100% | None | None | Continuous feeding (n=86) *compared with* bolus feeding (n=85) | Mean episodes of apnoea/day | WMD 14.0 [-0.2, 28.2] |
| Toce et al (*266*) RCT (LII) | Birth weight <1500 g | 100% | None | None | Continuous feeding (n=30) *compared with* bolus feeding (n=23) | Mean episodes of apnoea/day | WMD -0.6 [-1.99, 0.79] |
| Dsilna et al (*258*) RCT (LII) | Birth weight <1200 g, gestation 24–29 weeks | 100% | None | None | Continuous feeding (n=22) *compared with* bolus feeding (n=46) | Respiratory distress syndrome | RR 1.11 [0.85, 1.44] |
| | | | | | | Need for mechanical ventilatory support | RR 0.95 [0.68, 1.33] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

# 4. FEEDING SCHEDULES

## 4.1 Initiation of enteral feeding

Milk feeding is generally initiated in stable infants >32 weeks gestation in the first 24 hours of life. However, the optimal timing of initiation of enteral feeding in infants <32 weeks gestation has been disputed. Practice differs considerably in developed and developing countries. Trophic feeding or minimal enteral nutrition (also known as low-volume enteral feeding, gut priming, and early hypocaloric feeding) is utilized commonly in developed countries and is defined as any enteral milk feed in the first few days of life in subnutritional quantities (e.g. 5–10 ml/kg/day on the first day), with parenteral nutrition providing the remainder of the infant's nutrient needs. It has been suggested that trophic feeding can promote gut development and reduce the time to enteral and breastfeeding without the potential complications of high-volume feeding (*270*). In developing countries, total parenteral nutrition (TPN) has limited application and many clinicians put LBW infants on maintenance enteral feeds as quickly as possible on day 1. However, other health practitioners commence enteral feeding on day 2, after the infants have been assessed to be stable and not developing respiratory distress syndrome.

This section reviews the evidence for:

- trophic feeding or minimal enteral nutrition, beginning on day 1 with volumes of 5–10 ml/kg/day;
- initiation of 'maintenance' enteral feeding on day 1 with volumes >40ml/kg/day.

Intragastric feeding, oral feeding and direct breastfeeding are also considered.

### TROPHIC FEEDING OR MINIMAL ENTERAL NUTRITION

#### Results

A recently updated systematic review and meta-analysis (*271*) summarized 10 trials of trophic feedings compared with no feedings in pre-term infants <33 weeks gestation, and one trial which compared trophic feedings with advanced feedings.

### Effects on mortality and neurodevelopment

No studies were located which examined the impact on mortality or neurodevelopment.

### Effects on severe morbidity – necrotising enterocolitis

A meta-analysis of nine studies with 650 participants showed no significant difference in the incidence of necrotising enterocolitis among infants given trophic feedings or no feedings, although the findings do not exclude an important effect (RR 1.16, 95%CI 0.75 to 1.79) (*271*).

### Effects on malnutrition

No study examined the impact on standard deviation scores or malnutrition rates. In eight studies with 590 participants, the pooled effect on the number of days to regain birth weight was not significantly different in the trophic-feeding and no-feeding groups (WMD –0.44 days, 95%CI –1.32 to 0.44).

### Other important outcomes

Nine studies (617 participants) included in the meta-analysis by Tyson et al (*271*) examined the role of trophic feeding on the number of days to reach full enteral feeding, and six studies (370 participants) examined the duration of hospital stay. Trophic feeding resulted in significant benefits in both these outcomes. The WMD in number of days to reach full enteral feeding was lower by 2.55 days in the trophic feeding group (95%CI 0.99 to 4.12). The duration of hospital stay was shorter by 11.44 days among infants in the trophic-feeding group (95%CI 5.7 to 17.7).

## Conclusions and implications

The findings of this section are based on meta-analyses of RCTs from developed countries. Significantly less time to reach full enteral feeding was reported by the meta-analysis in the trophic-feeding group, but this group also had a higher incidence of necrotising enterocolitis although the difference was not statistically significant. However, the 95% confidence interval does not exclude an important increase in the risk of necrotising enterocolitis which could potentially outweigh any short- or long-term benefits of trophic feedings.

The studies included in the meta-analyses were heterogeneous and subject to observer and diagnostic surveillance bias. All studies were performed in pre-term infants <33 weeks gestation and even the meta-analysis had a limited sample size. All infants received supplemental intravenous fluids or parenteral feeds; the results are thus difficult to extrapolate to developing country settings where administration of intravenous fluids may not be available.

## Recommendations

No consensus statements or expert committee reports were located which examined the role of trophic feedings in LBW infants. Standard practice in some neonatal units is to provide trophic feedings in infants weighing <1500 g at birth in addition to total parenteral nutrition. This review was unable to provide additional recommendations due to insufficient evidence.

# INITIATION OF 'MAINTENANCE' ENTERAL FEEDING

## Results

### Effects on mortality

In the early 1960s, intravenous infusions were technologically not feasible for newborn infants and there was disagreement regarding the best time to administer full maintenance enteral fluids. A number of trials were conducted at this time to compare the effects of initiation of maintenance nasogastric feeds with no feeding on day 1 of life. Key studies include three trials from the US and UK in LBW infants, which are summarized in Table 4.1.1 (Level III-3 evidence and above) (*272–274*).

Cornblath et al randomized pre-term <1500 g infants into three groups who received different feeding regimens for the first 72 hours of life (*272*). The intravenous group received 65 ml/kg of 10% glucose intravenously for the first 24 hours of life and 75–85 ml/kg of 5%

glucose in 0.22% saline from 48 to 72 hours. The second group received nasogastric feeds of 60 ml/kg of 10% glucose in 12 equal feedings on day 1 and 80 ml/kg of 5% glucose in 0.22% saline in 8 equal feedings from 48 to 72 hours. The third group received no food or fluids on day 1 of life and enteral feedings (nasogastric glucose and half-strength formula) from 48 to 72 hours with 'the timing depending on the condition of the infant'.

Wharton and Bower randomized all infants <2250 g at birth to receive either early enteral feeds (starting within 4 hours of birth at 30 ml/kg on day 1 and progressing to 45 ml/kg on day 2, 60 ml/kg on day 3, and 75 ml/kg on day 4) or small-volume later enteral feeds (starting at 12–16 hours after birth at 8 ml/kg on day 1 and progressing to 16 ml/kg on day 2, 24 ml/kg on day 3, and 30 ml/kg on day 4) (*273*). The enteral feeds were undiluted breastmilk for infants <2000 g and half-cream evaporated milk for infants >2000 g. No intravenous fluids were provided and infants were fed 1–3 hourly depending on tolerance.

Smallpeice and Davies examined the impact of early feeding of human milk in 111 infants from 1000–2000 g admitted to the Radcliffe Infirmary in Oxford (*274*). These infants were fed within 2 hours of birth with 60 ml/kg on day 1 and progressed to 90 ml/kg on day 2, 120 ml/kg on day 3 and 150 ml/kg on day 4. Infants were fed 1–3 hourly depending on tolerance. Smallpeice and Davies also included 'comparison observations' made during the same 17-month period in infants who were born in the Churchill Hospital, Oxford. These infants were not fed until 4–32 hours after birth. While the majority of these infants had some feed during the first 24 hours, the amount and rate of increase over the 4 days was considerably less than in the Radcliffe group. No additional details were provided.

Cornblath et al reported lower mortality in the infants given IV fluids but no difference in death rates between the enterally fed infants and those given no food or fluids on the first day of life. Smallpeice and Davies also reported no significant difference between early and late enterally fed groups. However, Wharton and Bower reported a significant increase in mortality in the early enteral feeding group, compared to those fed smaller volumes from 12 to 16 hours. It is important to note that all these studies had major design flaws, including small sample sizes in all studies (*272–274*) and use of controls from a different hospital in one study (*274*) . Infants who became unwell during the study by Wharton and Bower were excluded. No studies were located which examined the impacts of early initiation of oral feeding in term LBW infants.

### Effects on malnutrition

Only two studies reported on the impact of early nasogastric feeding on growth parameters in LBW infants (Level III-3 evidence and above) (see summary Table 4.1.2) (*272*, *274*). Smallpeice and Davies indicated that there was a significant improvement in the time to regain birth weight in the early feeding group among infants 1000–2000 g at birth, but Cornbath reported no significant difference in mean weight gain. No study reported on malnutrition rates or standard deviation scores and no studies were located which examined the impacts of early initiation of oral feeding or breastfeeding in term LBW infants.

### Effects on other important outcomes

Three studies reported on the impact of early nasogastric feeding on *hypoglycaemia and hyperbilirubinaemia* in LBW infants (Level III-3 evidence and above) (see summary Table 4.1.3) (*272–274*). Mixed results were reported. No studies were located which examined the impacts of early initiation of oral feeding or breastfeeding in LBW infants, compared with delayed feeding.

## Conclusions and implications

Limited data are available from small trials during the 1960s in developed countries which examined the impact of early nasogastric feeding in pre-term infants. No study examined the role of early initiation of oral feeding or breastfeeding in infants with birth weights >2000 g. All studies had important design

flaws. The available results indicate that very pre-term infants may benefit from administration of intravenous fluids and avoidance of full enteral feeds on the first day of life.

There are no studies from developing country settings, where administration of intravenous fluids in all health facilities is less feasible and could be associated with higher risks.

## Recommendations

No policy statements from international or national organizations were located which examined the role of early initiation of 'maintenance' enteral feeding in the first 24 hours of life in infants <1500 g. Many neonatal units withhold enteral feeds in the first 24 hours of life in all infants <1500 g and give them intravenous fluids. Other units provide small enteral feeds to stable pre-term infants >1200 g on day 1 and monitor them closely. This review was unable to provide additional recommendations due to insufficient evidence.

**SUMMARY TABLE 4.1.1**
**Effects of initiation of maintenance enteral feeds in the first 24 hours of life on mortality rates**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Cornblath et al (*272*) RCT (LII) | Birth weight <1500 g | 100% | None | None | 60 ml/kg enteral glucose in the first 24 hours (n=30) *compared with* no food or fluids for the first 24 hours (n=30) | Mortality rate by day 14 | RR 1.00 [0.60, 1.66] |
| | | | | | 60 ml/kg enteral glucose in the first 24 hours (n=30) *compared with* intravenous 10% glucose 65 ml/kg in the first 24 hours (n=30) | Mortality rate by day 14 | RR 1.67 [0.87, 3.2] |
| Wharton & Bower (*273*) RCT (LII) | Birth weight <2250 g | 22% | 56% | 22% | Enteral milk feeds from 2–4 hours of birth, 30 ml/kg on day 1, increased to 75 ml/kg/day by day 4 (n=108) *compared with* enteral feeds started after 12–16 hours, 8 ml/kg/day increased to 30 ml/kg/day by day 4 (n = 116) | Mortality rate at hospital discharge | RR 2.93 [1.29, 6.67] |
| Smallpeice & Davies (*274*) Double cohort (LIII-3) | Birth weight between 1000 and 2000 g | 34% | 66% | None | Enteral milk feeds 60 ml/kg on the first day started from 2 hours of birth (n=111) compared to lower volume enteral feeds started after 4–32 hours of birth (n=45) | Mortality rate by day 28 | RR 0.91 [0.51, 1.64] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to have <32 wk gestation, those weighing 1501–2000 g to have 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## SUMMARY TABLE 4.1.2
### Effects of initiation of maintenance enteral feeds in the first 24 hours of life on growth outcomes in LBW infants

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Cornblath et al (*272*) (LII) | Birth weight <1500 g | 100% | None | None | 60 ml/kg enteral glucose in the first 24 hours (n=30) *compared with* no food or fluids for the first 24 hours (n=30) | Mean weight loss from 72–87 hours | MD 0.2 [sd not available] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## SUMMARY TABLE 4.1.3
### Key studies which examine the effects of initiation of maintenance enteral feeds in the first 24 hours of life on biochemical measures in LBW infants

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Cornblath et al (*272*) RCT (LII) | Birth weight <1500 g | 100% | None | None | 60 ml/kg enteral glucose in the first 24 hours (n=30) *compared with* no food or fluids for the first 24 hours (n=30) | Bilirubin concentration (mg/100 ml) at 72–87 hours of age | MD -1.8 [-2.6, -1.0] |
| | | | | | | Bilirubin concentration (mg/100 ml) at 72–87 hours of age | MD -7.0 [-10.3, -3.68] |
| Wharton & Bower (*273*) RCT (LIII-1) | Birth weight <2500 g | 22% | 56% | 22% | Enteral milk feeds from 2–4 hours of birth, 30 ml/kg on day 1, increased to 75 ml/kg/day by day 4 (n=108) *compared with* enteral feeds started after 12–16 hours, 8 ml/kg/day increased to 30 ml/kg/day by day 4 (n=116) | Hyperbilirubinaemia by hospital discharge (bilirubin concentration >15 mg/100ml) | RR 0.23 [0.03, 1.96] |
| | | | | | | Hypoglycaemia by hospital discharge (blood glucose <20 mg/100 ml) | RR 0.11 [0.01, 2.09] |
| Smallpeice & Davies (*274*) RCT (LIII-3) | Birth weight 1000– 2000 g | 34% | 66% | None | Enteral milk feeds 60 ml/kg on the first day started from 2 hours of birth (n=111) compared to lower volume enteral feeds started after 4–32 hours of birth (n=45) | Hyperbilirubinaemia by hospital discharge (bilirubin concentration >15 mg/100ml) | RR 0.23 [0.13, 0.40] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## 4.2 Progression and scheduling of enteral feeding

Scheduling of feeds is also a matter of some controversy. Some clinicians advocate rapid progression, while others increase the feeds slowly to reduce the risk of aspiration and feed intolerance. This section examines how much and how frequently to feed LBW infants. We first review how feeds from day 1 to day 7 should be managed and if the daily feeding volumes should be increased rapidly or slowly. We then consider feeding in the second week of life, examining the evidence on frequencies and intervals (i.e. when to change from 1, 2, 3 and 4-hourly feeding regimens), and when an infant should be given demand feeding.

The following issues are considered below:

- rapid versus slow progression of enteral feeding;
- volume of enteral feeds in the second week of life;
- feeding frequencies and intervals;
- demand or scheduled feeding.

### RAPID VERSUS SLOW PROGRESSION OF ENTERAL FEEDING DURING THE FIRST WEEK OF LIFE

This section examines the trials that compared the clinical impacts of different enteral fluid volume advancement rates in the first week of life (slow versus fast enteral feeding progression). All trials provided infants with intravenous fluids in addition to enteral feeds.

#### Results

Effects on mortality and neurodevelopment

No studies were located which examined the impact of enteral feeding progression on mortality rates or neurodevelopment in LBW infants.

#### Effects on serious morbidity – necrotising enterocolitis

A meta-analysis (*275*) of all available RCTs till year 2003 examined the impacts on necrotising enterocolitis (Level I evidence). In three US trials (*276–278*), the infants were provided with supplemental intravenous glucose or total parenteral nutrition (TPN). The meta-analysis demonstrated no significant effect of varying the rate (10–35 ml/kg/day) of feed advancement in infants <2000 g from day 2 to 7 on proven necrotising enterocolitis (Bell's stage II or greater) (see summary Table 4.2.1). In these trials there were no differences between groups in the incidence of proven necrotising enterocolitis, but the confidence intervals were wide. Another trial in 2004 randomized infants of birth weight 1000–2000 g to receive 30 ml/kg/day (rapid) or 20 ml/kg/day (slow advancement) (see summary Table 4.2.1) (*279*). This trial reported that three infants in the intervention group and two in the control group developed necrotising enterocolitis, but the difference was not statistically significant. No trial was located that examined the impact in infants who did not receive intravenous fluids.

One trial in VLBW infants (mean gestational age 28 weeks), who were given TPN for the first 10 days of life, compared trophic feedings (20 ml/kg/day for 10 days after initiation of feeds) with advancing the feeds (starting with 20 ml/kg/day and increasing every day by 20 ml/kg/day until 140 ml/kg/day)(*280*). The trial was stopped early because of the larger number of cases of necrotising enterocolitis in the group assigned to advancing feeding volumes (7 vs. 1, one-sided Fischer exact test value 0.03) (relative risk 7.1, 95%CI 0.9 to 56.2; risk difference 8.6%, 95%CI 1% to 16.1%).

#### Effects on malnutrition

This meta-analysis (*275*) examined the impacts on growth rates (Level I evidence) of the above three US trials (*276–278*). A significantly lower number of days to regain birth weight was detected in those infants who received rapid feeding progression (see summary Table 4.2.2). The impact on rates of malnutrition was not reported. Caple et al reported in a later trial that infants in the 30 ml/kg/day rapid advancement group regained the birth weight faster (Table 4.2.2) (*279*).

### Effects on other important outcomes

This meta-analysis (*275*) also examined the impacts on *time to reach full enteral feeds* (Level I evidence) of the same three US trials (*276–278*) (see Table 4.2.3) and concluded that rapid progression of feed advancement significantly reduced the time to reach full enteral feeds. Caple et al also reported that infants in the 30 ml/kg/day rapid advancement group had a reduced time to reach full enteral feeds (see summary Table 4.2.2) (*279*). Berseth et al reported that advancing the feeds reduced the time to reach full enteral feeding (shorter by 13.4 days, 95%CI 8.2 to 18.6) (*280*).

## Conclusions and implications

The findings of this section are based on meta-analyses of RCTs from developed countries and two subsequently published RCTs. The studies included in the meta-analyses were heterogeneous and subject to observer and diagnostic surveillance bias. All the infants received supplemental intravenous fluids or parenteral feeds so that the results are difficult to extrapolate to developing country settings where administration of intravenous fluids may not be feasible. The results show that fast rates of advancement of feeding (up to 35 ml/kg/day) may shorten the time to reach full enteral feeds and may increase weight gain but may increase the risk of necrotizing enterocolitis in infants of <32 weeks gestation. There is limited information regarding safety (broad confidence intervals for incidence of necrotising enterocolitis) and the effect on length of hospital stay.

### Infants <32 weeks gestation (or birth weights <1500 g if gestation is not available)

In infants 1000–1500 g, rapid progression of enteral feeding decreases the time to regain birth weight and may reduce the time till full enteral feeding. The limited information on safety suggests that rapid progression may be safe, but the wide confidence intervals do not exclude an important effect on necrotising enterocolitis. One RCT in pre-term infants with mean birth weight about 1000 g showed a higher risk of necrotizing enterocolitis even with "slow" progression of feeding (20 ml/kg/day) as compared to trophic feedings.

### Infants 32–36 weeks gestation (or birth weights 1500–2000 g if gestation is not available)

Only 20% of infants in the studies included in the meta-analyses were of this gestation period and thus it is difficult to draw any conclusions for this group. However, these infants are more robust and should accept rapid feeding regimens better than the more immature infants.

### Term LBW infants (or birth weights >2000 g if gestation is not available)

No data were available for this subgroup. However, these infants are developmentally mature and should tolerate full demand feeding from day 1 or 2.

## Recommendations

No policy statements from international or national organizations were located which examined the role of rapid progression of enteral feeding in LBW infants or enteral fluid rates or feeding regimens in LBW infants. Fluids are commonly provided at 60 ml/kg/day on day 1, with daily stepwise increments of up to 20 ml/kg/day for pre-term infants. Some units use a slower feeding progression (≤10 ml/kg/day for the first few days) for pre-term infants with birth weights <1200 g. Many units use developmental and clinical cues and gastric aspirates to decide on progression of feeds. This review supports these recommendations.

## SUMMARY TABLE 4.2.1
## Effects of rapid compared with slow fluid progression on necrotising enterocolitis in LBW infants

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Kennedy & Tyson (*275*) Meta-analysis of 3 RCTs (LI) | Birth weight <2000 g | 80% | 20% | None | Feeding volumes increased by 20–35 ml/kg/day (n=171) *compared with* feeding volumes increased by 10–20 ml/kg/day (n=191) | Proven necrotising enterocolitis (Bell's stage II or greater) | RR 0.90 [0.46, 1.77] |
| Caple et al (*279*) RCT (LII) | Birth weight 1000-2000 g | 80% | 20% | None | Feeding volumes increased by 30ml/kg/day (n=72) *compared with* feeding volumes increased by 20ml/kg/day (n=83) | Necrotising enterocolitis (Bell's stage IIA or greater) | RR 1.73 [0.3, 10.06] |
| Berseth et al (*280*) RCT (LII) | Birth weight <1500 g, given total parenteral nutrition for irst 10 days of life | 100% | None | None | Feeding volumes increased by 20 ml/kg/day (n=72) *compared with* feeding volumes not increased for 10 days (n=77) | Necrotizing enterocolitis | RR 7.1 [0.9, 56.2] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## SUMMARY TABLE 4.2.2
## Effects of rapid compared with slow fluid progression on growth outcomes in LBW infants

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Kennedy & Tyson (*275*) Meta-analysis of 3 RCTs (LI) | Birth weight <2000 g | 78% | 22% | None | Feeding volumes increased by 20–35 ml/kg/day (n=156) *compared with* feeding volumes increased by 10–20 ml/kg/day (n=179) | Days to regain birth weight | WMD -2.1 [-1.5, -3.0] |
| Caple et al RCT (LII) | Birth weight 1000–2000 g | 80% | 20% | None | Feeding volumes increased by 30 ml/kg/day (n=72) *compared with* feeding volumes increased by 20 ml/kg/day (n=83) | Days to regain birth weight | MD -5 [-8.0, 0.0] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**SUMMARY TABLE 4.2.3**
**Effects of rapid compared with slow fluid progression on time to reach full enteral feeds in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Kennedy & Tyson (*275*) Meta-analysis of 3 RCTs (LI) | Birth weight <2000 g | 78% | 22% | None | Feeding volumes increased by 20–35 ml/kg/day (n=156) *compared with* feeding volumes increased by 10–20 ml/kg/day (n=179) | Time to reach full enteral feeds | WMD -3.2 days [-4.1, -1.4] |
| Caple et al RCT (LII) | Birth weight 1000–2000 g | 80% | 20% | None | Feeding volumes increased by 30 ml/kg/day (n=72) *compared with* feeding volumes increased by 20 ml/kg/day (n=83) | Time to reach full enteral feeds | Difference in medians -3.0 days [-3.0, -2.0] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## VOLUME OF ENTERAL FEEDS IN THE SECOND WEEK OF LIFE

### Results

#### Effects on mortality, serious morbidity or neurodevelopment

No studies were located which examined the impact of feeding in the second week of life on mortality, serious morbidity, or neurodevelopment in LBW infants.

#### Effects on malnutrition

One Australian RCT (Level II evidence) was located which compared the impacts of two different feeding regimens (150 ml/kg/day compared to 200 ml/kg/day) from the time full enteral feeds were tolerated at day 7–14 in infants <30 weeks gestation (*281*). Daily weight gains and weights and arm fat area at 35 weeks were significantly higher in the high volume compared to the low volume group. However, there was no difference in length or head circumference at 35 weeks and no difference in any growth parameter at 1 year of age. Impacts on malnutrition or weight-for-age standard deviation scores were not reported. No information regarding the timing of initiation of demand feeding or hospital discharge was reported in this study.

### Conclusions and implications

Only one small RCT was located which compared the administration of different daily fluid volumes in the second week of life in infants who were <30 weeks gestation at birth (Level II evidence). This trial reported variable short-term impacts on different outcomes and no long-term impact on growth parameters at 1 year of age. Overall, no implications can be drawn for infants of particular gestational ages or birth weights.

### Recommendations

No policy statements from international or national organizations were located which provided recommendations for feeding beyond the first week of life in LBW infants. Feeds are commonly provided in neonatal units in the second week of life in increments until 180–200 ml/kg/day of fluid intake is reached. It was not possible to provide additional recommendations due to insufficient evidence.

## FEED FREQUENCIES AND INTERVALS

### Results

#### Effects on mortality, serious morbidity, neurodevelopment or malnutrition

No RCTs or observational studies were located which examined the impact of feeding frequencies or intervals on mortality, serious

morbidity, neurodevelopment or malnutrition in LBW infants.

### Effects on other important outcomes

Only case series and descriptive studies were located which examined outcomes such as *feed tolerance* and *biochemical measures* (Level IV evidence) (*270*, *282*). These studies indicated that feeding regimens such as 4-hourly feeds for infants >2000 g, 3-hourly for infants 1500–2000 g, 2-hourly for infants 1000–1500 g, and hourly in infants <1000 g were well tolerated, promoted biochemical stability, and produced minimal gastric aspirates.

Evidence for increasing feed intervals is even less well documented. Only one case series was located and demonstrated that increasing the feed interval on a weekly basis can be well tolerated in LBW infants (*270*).

## Conclusions and implications

Only case series and descriptive studies were located in this section. These describe the safe implementation of standard regimens as monitored by biochemical and physiological outcomes. However, no comparative studies were available to allow decisions to be made about the safest or most effective regimens. No implications can be drawn for infants of particular gestational ages or birth weights.

## Recommendations

No policy statements from international or national organizations were located which examined the frequency of feeding in LBW infants. Standard practice in many neonatal units is to commence feeding 4-hourly for infants >2000 g, 3-hourly for infants 1500–2000 g, 2-hourly for infants 1000–1500 g, and hourly in infants <1000 g. Feeding intervals are then extended on an individual basis depending on feed tolerance, gastric aspirates and physiological stability. It was not possible to provide additional recommendations due to insufficient evidence.

# DEMAND OR SCHEDULED FEEDING

## Results

### Effects on mortality, serious morbidity, neurodevelopment or malnutrition

No studies were located which examined the influence that the timing of demand feeding may have on mortality, serious morbidity, or malnutrition in LBW infants.

### Effects on other important outcomes

An integrated review of eight studies evaluated the impact of demand feeding in pre-term infants (*283–290*). The studies employed a variety of research methods including non-experimental, quasi-experimental, and experimental designs. The earliest studies are difficult to interpret due to inadequate sample sizes and incomplete descriptions of methodology. Trials from the 1980s and early 1990s were better described; however, their interventions were facilitator-dependent and difficult to replicate. Overall, the integrated review indicated that pre-term infants who were fed on demand had a *shorter duration of hospitalization* and had *weight gains* that were equivalent to or greater than non-demand-fed infants.

## Conclusions and implications

There is limited evidence that demand feeding of LBW infants reduces the duration of hospitalization. All studies had methodologic weaknesses and most analyses also suffered from a significant lack of statistical power. Overall, no implications can be drawn for infants of particular gestational ages or birth weights.

It may be advantageous to start demand feeding as early as possible in developing countries because of the costs and risks of prolonged hospitalization. However, demand feeding initially requires more monitoring and training as feeding and hunger cues in LBW infants must be detected by health professionals and care is needed with weight monitoring.

## Recommendations

No policy statements from international or national organizations were located which examined the timing of demand feeding in

LBW infants. Decisions about when a LBW infant should begin demand feeding are currently made on the basis of an individual infant's developmental maturity. Cues include conscious state and the ability of the infant to wake spontaneously for feeds and respond to hunger by crying. Standard practice in many neonatal units is to progress to demand feeding when infants can tolerate 3–4 hourly feeds, are stable and alert, and have no problems with hypoglycaemia. Kangaroo mother care (KMC) guidelines include rousing LBW infants for feeding if the baby sleeps longer than 2–3 hours in order to prevent hypoglycaemia. It was not possible to provide additional recommendations due to insufficient evidence.

# 5. SUPPORT

## 5.1 Supportive care for the LBW infant

Warmth, developmental care and food are basic, interrelated needs for the LBW infant. Infants who are not nurtured and stimulated grow poorly, while hypothermic infants have feeding difficulties and may utilize calories to produce heat. Interventions that reduce hypothermia and promote development are integral to the nutritional status and health outcomes of all LBW infants.

The following interventions are reviewed in this section:

(1) Kangaroo mother care or only skin-to-skin contact;
(2) Non-nutritive sucking;
(3) Maternal participation in caring for LBW infants in hospital;
(4) Timing and criteria for hospital discharge.

### (1) KANGAROO MOTHER CARE OR ONLY SKIN-TO-SKIN CONTACT

Skin-to-skin contact is defined as any contact between the mother's and the infant's skin over any period of time, usually commencing immediately after birth. Kangaroo mother care (KMC) was first described in the late 1970s as an alternative to the conventional contemporary method of care for LBW infants. The major components of KMC are: skin-to-skin contact (i.e. infants are kept, day and night, between the mother's breasts firmly attached to the chest in an upright position), frequent and exclusive breastfeeding, and early discharge from hospital regardless of weight or gestational age.

#### Results

##### Effects on mortality

No studies were located which examined the impact of only skin-to-skin contact on mortality rates. Two RCTs were located that examined the effect of KMC, compared to conventional care, in stabilized LBW infants on the risk of mortality (Level II evidence); these are summarized in Table 5.1.1 (*291–293*). Both studies randomized infants of birth weight 1500–2000 g and were conducted in developing countries; one was a multi-centre study from Ethiopia, Mexico and Indonesia, and the other was a larger trial from Colombia. Cattaneo et al followed up infants till hospital discharge only, while Charpak et al completed follow-up till 12 months of age. The findings from these studies suggest that KMC may be at least as effective as conventional care in reducing mortality rates in eligible infants. Definitive conclusions cannot be made because of the wide confidence intervals. It should be noted that less than half of the <2000 g infants were eligible for KMC according to the inclusion criteria. Most of the mortality in this group occurred before the infants became eligible for KMC.

A recently published RCT from Ethiopia enrolled babies <2000 g before stabilization around 10 hours after birth (*294*). A little less than half of all babies born in the hospital with birth weights <2000 g during the study period were included in the study. Lower mortality rates were reported in the KMC group, compared with the conventional method of care group (RR 0.59, 95%CI 0.34 to 1.04). These results are consistent with two previous observational studies from Zimbabwe (*295*) and Mozambique (*296*), which initiated KMC

for all babies <1800 g without any stabilization in incubators. In the Zimbabwean cohort study, mortality among 126 KMC babies was lower than historical controls (improvement from 50–10%). In the cross-sectional study from Mozambique, mortality was reported to be lower in 22 KMC babies, compared with 10 babies who could not be provided KMC because the mother was not available or there was no room in the KMC ward (mortality 20% in KMC infants, compared to 73% in non-KMC infants, p <0.01). It is important to note that both of these studies had small sample sizes and methodological flaws (including insufficient blinding and losses to follow-up). In addition, the study by Bergman et al compared the outcomes to a historical control group with insufficient adjustment for confounding factors. No longer-term impacts after hospital discharge were reported.

### Effects on serious morbidity – serious illness/infection

Three RCTs, which examined the impact of KMC on serious illness or infection (Level II evidence), are summarized in Table 5.1.2 (*291–293, 297*). All three trials were of moderate to poor methodological quality (with a large proportion of drop-outs and loss to follow-up), two were the studies discussed above, and the third was implemented in Ecuador (*297*). One of the studies showed a significant reduction in nosocomial infections and the other a significant reduction in episodes of severe illness during the first 6 months of life (*292*, *297*). No studies were located which examined the impact of skin-to-skin contact only on serious morbidity.

### Effects on neurodevelopment

Only Charpak et al evaluated the impacts on neurodevelopment (Level II evidence) (see Table 5.2.3) (*292*, *293*). He reported that there was no significant difference between KMC and conventional care in mean Griffith's quotient at 6 and 12 months of corrected age. There was no longer-term follow-up (see summary Table 5.1.3). No studies were located which examined the impact of skin-to-skin contact only on neurodevelopmental outcomes.

### Effects on malnutrition

All three RCTs described above evaluated the differences on growth rates (Level II evidence), but none evaluated the impacts on standard deviation scores or malnutrition (*291–293*, *297*). No significant differences, compared to conventional care, were reported on any growth parameters except for one trial which reported that KMC infants gained slightly more weight per day by the time of discharge, compared with the controls (WMD 3.6 g/d, 95%CI 0.78 to 6.42), and had a larger head circumference at 6 months corrected age (0.34 cm, 95%CI 0.11 to 0.57) (*291*).

### Effects on other important outcomes

Three RCTs were located which evaluated the impact of KMC on breastfeeding rates (Level II evidence) (*291–293*, *297*). These trials have been described above and are summarized in Table 5.1.4. Improvements in exclusive breastfeeding (EBF) at the time of hospital discharge and in any breastfeeding up to 3 months of corrected age were reported in two of the trials in KMC infants (*291–293*). A meta-analysis of two studies (*291*, *297*) showed no significant difference in EBF at 1 month follow-up (RR 0.77, 95%CI 0.49 to 1.23) (*298*).

A meta-analysis of studies in healthy full-term babies has shown that early skin-to-skin contact is associated with higher breastfeeding rates at 1–3 months, compared with standard contact (OR 2.15, 95%CI 1.10 to 4.22) (*299*). A subsequent study in healthy, full-term infants showed that skin-to-skin contact with the mother starting 15–20 minutes after birth for one hour was associated with sleeping longer, more flexor movements and postures and less extensor movements in observations starting four hours after birth (*300*). In addition, two small studies in LBW infants (one RCT and one cohort study) (Level III-3 evidence and above) examined the impact of skin-to-skin contact alone in LBW infants on breastfeeding patterns (*301*, *302*). Both studies detected a significant impact on breastfeeding rates. In the study by Whitelaw et al, mothers randomized to a skin-to-skin contact group lactated for 4 weeks longer on average than the control

group, and at 6 months of age the skin-to–skin contact group of infants was reported to cry significantly less than the control group. In the study of Hurst et al, skin-to-skin contact infants were reported to have a strong linear increase in milk volume in contrast to no indicative change in the control group's milk volume. It is important to note that both these studies had small sample sizes and methodological flaws (including insufficient blinding and losses to follow-up). In addition, the study by Hurst et al compared the outcomes to a historical control group with insufficient adjustment for confounding factors. No longer-term impacts after hospital discharge were reported.

Another RCT compared skin-to-skin contact from birth with conventional incubator care on *physiological parameters* during the first 6 hours of life in babies weighing 1200–2199 g (*303*). Thirty-five LBW infants (1200-2199 g) from two secondary-level referral hospitals in South Africa were included in the study over a period of 8 months. Of the infants included in the analysis, 3/18 in the skin-to-skin contact group, compared with 12/13 in the conventional care group, exceeded the pre-determined parameters of stability ($P < 0.001$); stabilization scores in the two groups respectively were 77.11 and 74.23, mean difference 2.88 ($P = 0.031$). All 18 babies in the skin-to-skin contact group were stable in 6 hours, compared with 6/13 incubated infants.

A pilot test of a *community-based feasibility* of KMC has been reported from Bangladesh (*304*). Of the 35 post-partum women who were taught KMC in the community, 77% initiated skin-to-skin contact and 85% of them with LBW babies did so (37% were LBW infants); 66% provided skin-to-skin contact most of the time during the first two days, and 45% during the first week. These mothers delayed bathing the newborn but few slept upright with the newborn; 17% of the babies were taken to a health facility due to illness. KMC was quickly adopted by the community.

### Conclusions and implications

Most of the available studies are from developing countries. Effective KMC requires appropriate skills and support but could be very useful in resource-poor settings. Limited data on its efficacy are available. Most studies only included stabilized LBW infants. There is some evidence that KMC can also be used in unstabilized infants in resource-poor settings. The available evidence suggests that KMC is at least as effective as conventional care in eligible infants in reducing mortality. It may have benefits over conventional care in reducing infections, and in improving weight gain and exclusive breastfeeding during hospital stay. Community-based KMC has been tried successfully in some settings, but more data are needed on its efficacy. There seems to be no evidence to suggest that KMC or skin-to-skin contact is unsafe and should not be used, especially in environments without access to any other forms of thermal care. No data were available for term SGA infants.

#### Infants <32 weeks gestation (or birth weights <1500 g if gestation is not available)

There was no clear evidence regarding the effect of KMC in these infants. Many of them were excluded due to instability.

#### Infants 32–36 weeks gestation (or birth weights 1500–2000 g if gestation is not available)

In stable infants between 32 and 36 weeks gestation, there is evidence that KMC is at least as effective as conventional care in reducing mortality. There may be benefits in terms of reducing infections and in improving exclusive breastfeeding rates and weight gain. However, the impact among unstable infants of these gestational ages is unclear.

#### Term LBW infants (or birth weights >2000 g if gestation is not available)

There are no data regarding the effect of KMC in these infants.

## Recommendations

A recent publication from WHO (*305*) promotes the role of KMC in stable LBW infants in resource-poor countries. KMC and skin-to-skin contact are standard practice in many neonatal units and health facilities in resource-poor areas, especially those without access to incubators and radiant heaters. The findings of this review support these recommendations.

**SUMMARY TABLE 5.1.1**
**Effects of Kangaroo mother care compared with conventional care on mortality in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Cattaneo et al (*291*) RCT (LII) | Birth weight 1000–2000 g. Stable infants only. | 14% | 86% | None | Kangaroo mother care (n=149) *compared with* conventional care (n=136) | Mortality before hospital discharge | RR 0.91 [0.19, 4.45] |
| Charpak et al (*292*) RCT (LII) | Birth weight <2000 g. Stable infants only. | 12% | 88% | None | Kangaroo mother care (n=364) *compared with* conventional care (n=345) | Mortality at 40–41 wks gestational age | RR 0.59 [0.21, 1.55] |
| Charpak et et al (*293*) RCT (LII) | Birth weight <2000 g. Stable infants only. | 12% | 88% | None | Kangaroo mother care (n=350) *compared with* conventional care (n=343) | Mortality at 12 months chronological age | RR 0.57 [0.27, 1.17] |
| Worku & Kassie (*294*) RCT (LII) | Birth weight <2000 g. Stable or unstable infants starting around 10 hours of birth. | | | | Kangaroo mother care (n=62) *compared with* conventional care (n=61) | Mortality before hospital discharge | RR 0.59 [0.34, 1.04] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**SUMMARY TABLE 5.1.2**
**Effects of Kangaroo mother care compared with conventional care on severe morbidity in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Cattaneo et al (*291*) RCT (LII) | Birth weight 1000– 2000 g. Stable infants only. | 14% | 86% | None | Kangaroo mother care (n=149) *compared with* conventional care (n=136) | Episodes of severe infection up to hospital discharge | RR 0.63 [0.33, 1.21] |
| Charpak et al (*292*) RCT (LII) | Birth weight <2000 g. Stable infants only. | 12% | 88% | None | Kangaroo mother care (n=343) *compared with* conventional care (n=320) | No. of infectious episodes requiring hospital treatment up to 40–41 weeks gestational age | RR 0.69 [0.43, 1.12] |
| | | | | | | Nosocomial infections up to 40–41 weeks gestational age | 0.49 [0.25, 0.93] |
| Charpak et al (*293*) RCT (LII) | Birth weight <2000 g. Stable infants only. | 12% | 88% | None | Kangaroo mother care (n=325) *compared with* conventional care (n=305) | No. of infectious episodes requiring hospital treatment at up to 12 months age | RR 0.86 [0.71, 1.03] |
| Sloan et al (*297*) RCT (LII) | Birth weight <2000 g. Stable infants only. | 20% | 80% | None | Kangaroo mother care (n=140) *compared with* conventional care (n=160) | Episodes of severe illness up to 40–41 weeks gestational age | RR 0.30 [0.14, 0.67] |
| | | | | | Kangaroo mother care (n=131) *compared with* conventional care (n=152) | Episodes of severe illness up to 6 months age | RR 0.30 [0.14, 0.61] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501-–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**SUMMARY TABLE 5.1.3**
**Effects of Kangaroo mother care compared with conventional care on neurodevelopment in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Charpak et al (*293*), RCT (LII) | Birth weight <2000 g. Stable infants only. | 12% | 88% | None | Kangaroo mother care (n=308) *compared with* conventional care (n=271) | Psychomotor development (Griffith quotients) at 12 months corrected age | WMD 1.05 [-0.75, 2.85] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**SUMMARY TABLE 5.1.4**
**Effects of Kangaroo mother care compared with conventional care on breastfeeding patterns in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Outcome measure | Comparison groups | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Cattaneo et al (*291*) RCT (LII) | Birth weight 1000–2000 g. Stable infants only. | 14% | 86% | None | Kangaroo mother care (n=146) *compared with* conventional care (n=133) | No EBF at discharge | RR 0.41 [0.25, 0.68] |
| | | | | | Kangaroo mother care (n=93) *compared with* conventional care (n=82) | No EBF at 1 month follow-up | RR 0.77 [0.46, 1.29] |
| Charpak et al (*292*) RCT (LII) | Birth weight <2000 g. Stable infants only. | 12% | 88% | None | Kangaroo mother care (n=343) *compared with* conventional care (n=320) | No EBF at 40–41 weeks gestational age | RR 0.98 [0.85, 1.13] |
| Charpak et al (*293*) RCT (LII) | Birth weight <2000 g. Stable infants only. | 12% | 88% | None | Kangaroo mother care (n=320) *compared with* conventional care (n=305) | Any BF at 3 months corrected age | RR 1.08 [1.01, 1.18] |
| Sloan et al (*294*) RCT (LII) | Birth weight < 2000 g. Stable infants only. | 20% | 80% | None | Kangaroo mother care (n=93) *compared with* conventional care (n=111) | No EBF at 1 month follow-up | RR 0.80 [0.29, 2.15] |
| | | | | | Kangaroo mother care (n=66) *compared with* conventional care (n=80) | No EBF at 6 month follow-up | RR 1.01 [0.90, 1.13] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## (2) NON-NUTRITIVE SUCKING

Non-nutritive sucking refers to sucking without oral fluid intake, e.g. when a 'dummy' or 'pacifier' is used. Another reported method is sucking on the 'emptied' breast. Non-nutritive sucking has been postulated to improve breastfeeding and to shorten the time to oral feeding in pre-term infants.

### Results

#### Effects on mortality, serious morbidity and neurodevelopment

No studies were located which examined the influence of non-nutritive sucking on mortality, serious morbidity and neurodevelopment in LBW infants.

#### Effects on malnutrition

In a meta-analysis of all available RCTs till the year 2003 (Level I evidence), three trials in the US (see Table 5.1.5) demonstrated no significant advantage from non-nutritive sucking among infants <1800 g in terms of weight gain per day until hospital discharge (*306*). Field's trial demonstrated a trend favouring the control group (*307*), but the other two showed no difference between the groups (*308*, *309*). The results are difficult to interpret as all the studies were of poor methodological quality with small sample sizes. No impacts on standard deviation scores or malnutrition were identified.

#### Effects on other important outcomes

Another meta-analysis (Level I evidence), in which two trials in the US (see Table 5.1.6) were included (*307*, *310*), demonstrated a significant advantage in providing infants <1800 g with non-nutritive sucking on duration of hospital stay (*306*). However, the indi-

**SUMMARY TABLE 5.1.5**
**Effects of non-nutritive sucking compared with conventional care on growth outcomes in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Pinelli et al (*306*) Meta-analysis of 3 RCTs (LI) | Birth weight <1800 g | 58% | 42% | None | Non-nutritive sucking (n=59) *compared with* conventional care (n=58) | Weight gain (grams per day) | WMD 1.57 [-0.37, 3.50] |

* If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**SUMMARY TABLE 5.1.6**
**Effects of non-nutritive sucking compared with conventional care on hospitalization rates in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Outcome measure | Comparison groups | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Pinelli et al (*306*) Meta-analysis of 2 RCTs (LI) | Birth weight <1800 g | 58% | 42% | None | Non-nutritive sucking (n=44) *compared with* conventional care (n=43) | Length of hospital stay in days | WMD -7.1 [-12.6, 1.7] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

vidual trials reported conflicting results and were of poor methodological quality (small sample sizes and inadequate allocation concealment). In particular, Field found no difference between the groups, but Bernbaum et al demonstrated a significant reduction in length of hospital stay. A small study in 32 babies with an average gestation of 33 weeks examined the effect of suckling at the breast (after as much milk as possible had been expressed) on breastfeeding rates after discharge from the hospital. The infants in the intervention group had longer durations of exclusive breastfeeding (WMD 1.8 months, 95%CI 1.1 to 2.5) and total breastfeeding (WMD 1.8 months, 95%CI 0.3 to 3.3).

### Conclusions and implications

The results indicate that non-nutritive sucking may decrease the length of hospital stay in pre-term infants, but has no effect on growth outcomes in pre-term infants who weigh <1800 g at birth. The results are difficult to interpret owing to the small sample sizes and other methodological flaws. There is lack of data on safety with regard to an increased risk of infections with pacifiers and dummies in resource-poor settings. Sucking on the emptied breast might provide sucking experience for LBW infants without interfering with their nutritional intake and without increased risk of infection.

### Recommendations

No consensus statements or expert committee reports were located which examined the role of non-nutritive sucking in LBW infants. It was not possible to provide recommendations due to insufficient evidence.

## (3) MATERNAL PARTICIPATION IN CARING FOR LBW INFANTS IN HOSPITAL

### Results

In this section, the effects of maternal participation in caring for LBW babies in hospital are summarized. Three studies from south Asia were identified. Karan and Rao studied the effects of a change in nursery policy towards

increased maternal participation in the care and feeding of infants <1800 g, using a before-after comparison (*311*). Narayanan et al followed up two groups with 25 LBW infants in each; the mothers of the first group of infants stayed in the neonatal care unit, while those in the second group were separated from their infants (*312*). Bhutta et al reported the effects of establishment of a step-down unit where the mothers provided all basic nursing care for their infants (<1500 g at birth) before being discharged under supervision, using a before-after comparison (*313*).

### Effect on mortality, morbidity, neurodevelopment or growth

None of the identified studies reported the effect of maternal participation on mortality rates, morbidity, neurodevelopment or growth.

### Other important outcomes

Maternal participation in the care of pre-term infants in hospital-based newborn care units was reported to lead to *early discharge* in all three studies (*311–313*). Bhutta et al reported that maternal participation in a step-down unit resulted in earlier discharge of VLBW infants (hospital stay before and after the establishment of the step-down unit was 34 ± 18 days and 16 ±14 days, respectively) without any increase in short-term complications or readmissions (*313*). Narayanan et al reported that the group of infants whose mothers had participated in caring and feeding during hospitalization had a significantly higher breastfeeding rate at 2.5 months postnatal age, compared with the group whose mothers had been separated from them (80% vs. 20%, $p < 0.05$) (*312*).

## Conclusions and implications

The results indicate that maternal participation in the care and feeding of hospitalized LBW infants led to improved mother's confidence in providing care, earlier discharge from hospital, and improved breastfeeding rates.

## Recommendations

No consensus statements or expert committee reports were located which examined the role of maternal participation in the care of LBW infants. It is standard practice in many neonatal units in developed and developing countries to involve mothers in the care and feeding of their LBW infants. The findings from this review support these recommendations.

# (4) TIMING AND CRITERIA FOR HOSPITAL DISCHARGE

## Results

This section summarizes the evidence related to the optimal duration of stay in the hospital for pre-term babies. Until about 1980, the traditional policy was to delay the discharge of pre-term infants until a pre-determined weight (2000 g or more) had been achieved. For many VLBW babies this implied several weeks of hospital stay. However, prolonged hospitalization is associated with an increased risk of contracting infections, delays in mother-child bonding, and higher costs. Early discharge is a component of KMC (described above) and is not discussed in this section.

Eight RCTs were located which examined the effect of early discharge of LBW infants on outcomes such as mortality, re-hospitalization, weight gain, and breastfeeding rates after discharge (*314–321*). The criteria for early discharge used in these studies included: baby able to breastfeed or bottle-feed (full oral feeds); baby able to maintain body temperature in an open crib; no evidence of clinical illness or serious apnoea; no weight loss; mother demonstrated satisfactory care-taking skills; and adequate physical environment for home care of the infant.

### Effect on mortality

Only one RCT (Level II evidence) reported the effect of early discharge (when no weight loss, partial or full oral feeds; n = 28), compared with conventional discharge (when gaining weight, crossed birth weight, and fully accepting oral feeds; n = 39) (*314*). The mortality up to 3 months postnatal age was similar in the

two groups (RR 0.80, 95%CI 0.26, 2.46), but the wide confidence intervals do not allow any firm conclusions.

### Effect on serious morbidity

Six RCTs, summarized in Table 5.1.7, examined the effect of early discharge on subsequent re-hospitalizations (*315–320*). None of the studies reported any significant difference between early and conventional discharge groups. Although the confidence intervals of all the individual studies were wide, most reported relative risks below 1 or close to 1.

### Effect on neurodevelopment

There were no studies that examined the effect of early discharge on neurodevelopment.

### Effect on malnutrition

Five RCTs, summarized in Table 5.1.8, examined the effect of early discharge on subsequent *weight gain* (*315*, *316*, *318*, *320*, *321*). None of the studies reported any significant difference between early and conventional discharge groups. No studies reported on malnutrition rates.

### Effect on other important outcomes

The RCT by Gunn et al also compared the effect of early discharge (full oral feeds but not yet gaining weight, n = 148) with routine discharge (full oral feeds and also gaining weight, n =160) on breastfeeding rates at 6 weeks and 6 months after discharge (Table 5.1.9) (*319*). The rate of any breastfeeding at 6 weeks (RR 0.91, 95%CI 0.75 to 1.11) or 6 months (RR 0.99, 95%CI 0.73 to 1.33) after discharge was not significantly different in the two groups.

A meta-analysis examined the effects of a policy of early discharge of stable pre-term infants with home support of intragastric feeding, compared with a policy of discharge of such infants when they had reached full oral feeds (*322*). Only one quasi-randomized trial with 88 infants was identified (*323*). It reported a lower risk of infection during the home intragastric feeding period, compared with the corresponding time in hospital for the control group (RR 0.35, 95%CI 0.17 to 0.69). There was no significant difference between groups in the duration and extent of breastfeeding, weight gain, and re-admission within 12 months post-discharge.

## Conclusions and implications

The results indicate that early discharge of LBW infants (on full oral feeds, able to maintain body temperature in an open crib, no clinical illness or serious apnoea or weight loss, and the mothers have satisfactory care-giving skills) is not associated with adverse outcomes and may have advantages in terms of cost savings. No conclusions can be drawn about the safety of discharging pre-term infants still on intragastric feeds.

Most of the studies were from developed countries. Experience from some developing countries (e.g. Pakistan, Bhutta et al., *313*) suggests that the findings are generally applicable to these settings also. The high risk of nosocomial infections in developing countries may make it even more important to discharge infants early. However, the lack of health facilities and follow-up support in the community is a significant challenge in most countries.

## Recommendations

International groups recommend early discharge of pre-term infants when the babies are gaining weight, maintaining temperature, are competent at suckle feeding and physiologically mature, and with family and community readiness to provide the necessary support for their home care (*11*). There were no consensus statements or expert committee reports located which examined the role of maternal participation in the care of LBW infants. It is standard practice in many neonatal units in developed and developing countries to discharge pre-term infants when they are stable and on full oral feeds. The findings of this review support these recommendations.

**SUMMARY TABLE 5.1.7**
**Effects of early compared with conventional discharge of LBW infants on hospital re-admission rates after discharge**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Dillard et al (*315*) RCT (LII) | Birth weight <2268 g | 15% | UK | UK | Early discharge: at least 2000 g, weight gain and absence of acute illness (n=183) *compared with* conventional discharge: weight at least 2268 g, weight gain and absence of acute illness (n=198) | Hospital re-admission within 4 weeks of discharge | RR 0.87 (0.35, 2.15) |
| Lefebvre et al (*316*) Double cohort (LIII-3) | Birth weight <2000 g | 50% | 45% | 5% | Early discharge: clinically well, outgrown their birth weight, full oral feeding, maintain body temperature, mother capable of caring for the infant (n=21) *compared with* conventional discharge at weight 2200–2400 g | Hospital re-admission from discharge to term | RR 1.62 (0.34, 7.8) |
| Brooten et al (*317*) RCT (LII) | Birth weight <1500 g | 66% | 34% | None | Early discharge when full oral feeding, maintenance of temperature, no serious apnoea and mother able to care for the baby (n=39) *compared with* conventional discharge at 2200 g weight (n = 40) | Hospital re-admission within 14 days of discharge<br>Hospital re-admission within 18 months of discharge | RR 0.82 (0.24, 2.83)<br>RR 1.03 (0.48, 2.19) |
| Casiro et al (*318*) RCT (LII) | Birth weight <2000 g | 50% | 30% | 20% | Early discharge: clinically well with no serious apnoea, full oral feeds, maintains body temperature and mother able to care for the baby (n=50) *compared with* conventional discharge at discretion of the attending physician (n=50) | Hospital re-admission within the first year of life | RR 1.14 (0.45, 2.91) |
| Gunn et al (*319*) RCT (LII) | Pre-term infants | 40% | 60% | None | Early discharge: full oral feeds but not yet gaining weight (n=148) *compared with* routine discharge when on full oral feeds and also gaining wt (n=160) | Hospital re-admission within 6 weeks after discharge | RR 0.74 (0.38, 1.44) |
| Cruz et al (*320*) RCT (LII) | Very low birth weight infants | 100% | None | None | Early discharge (n=27) *compared with* conventional discharge (n=16) | Infection rates | No significant difference |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**SUMMARY TABLE 5.1.8**
**Effect of early discharge compared with conventional discharge of LBW infants on growth outcomes after discharge**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Dillard et al (*315*) RCT (LII) | Birth weight <2268 g | 15% | UK | UK | Early discharge: at least 2000 g, weight gain and absence of acute illness (n=183) *compared with* conventional discharge: weight at least 2268 g, weight gain and absence of acute illness (n=198) | Weight gain at 4 weeks from discharge | MD -0.04 kg (p>0.1)[b] |
| Davies et al (*321*) RCT (LII) | Gestation <33 weeks | 95% | 5% | None | Early discharge (n=20) *compared with* conventional discharge (n=20) | Weight at MD term<br>Weight at 3 months beyond term | -0.07 kg (-0.37, 0.23)<br>MD -0.24 kg (-0.86, 0.37) |
| Lefebvre et al (*316*) Double cohort (LIII-3) | Birth weight <2000 g | 50% | 45% | 5% | Early discharge: clinically well, outgrown their birth weight, full oral feeding, maintain body temperature, mother capable of caring for the infant (n=21) *compared with* conventional discharge at weight 2200–2400 g | Weight at term | MD -0.05 kg (-0.33, 0.23) |
| Casiro et al (*318*) RCT (LII) | Birth weight <2000 g | 50% | 30% | 20% | Early discharge: clinically well with no serious apnoea, full oral feeds, maintains body temperature and mother able to care for the baby (n=50) *compared with* conventional discharge at discretion of the attending physician (n=50) | Weight at 1 year | MD 0.1 kg (-0.34, 0.54) |
| Cruz et al (*320*) RCT (LII) | Very low birth weight infants | 100% | None | None | Early discharge (n=27) compared with conventional discharge (n=16) | Weight gain | No significant difference |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.
[b] Standard deviations not provided, thus confidence intervals not calculated.

## 5.2 Support for the breastfeeding mother

The importance of providing mother's own milk to LBW infants has been described in previous sections. The following interventions to improve breastfeeding rates in mothers of pre-term and term LBW infants have been reviewed:

- Breastfeeding counselling
- Drug therapy
- Breast milk supplementer.

### BREASTFEEDING COUNSELLING

A meta-analysis of 20 randomized or quasi-randomized trials involving 23,712 mother-infant pairs (infants with any birth weight, four trials specifically excluded LBW), showed that professional support was effective in increasing the rates of any breastfeeding at 6 months (RR0.89, 95%CI 0.81 to 0.97), but its effect on EBF was not significant. Lay support was effective in increasing EBF rates (RR0.66, 95%CI 0.49 to 0.69), but its effect on any breastfeeding was not significant (*324*). The few studies among LBW infants that were located are summarized below.

### Results

#### Effects on mortality and neurodevelopment

No studies were identified which examined the influence of breastfeeding counselling on mortality and neurodevelopment in LBW infants.

#### Effects on malnutrition

Two RCTs were located that examined the impacts of breastfeeding counselling in LBW infants (*187*). One large RCT was located which examined the impacts of breastfeeding on malnutrition rates in a subset of predominantly SGA LBW Indian infants (Level II evidence, see summary Table 5.2.1) (*187*, *325*). The trial by Bhandari et al compared the impact of counselling mothers in EBF at multiple opportunities (including immunization sessions, illness contacts, women's group meetings, and home visits) with routine care. Rates of EBF at 3 months of age increased (see below) and no significant disadvantages were detected in mean weight, mean length, height-for-age (<2 z scores) or weight-for-height (<2 z scores) in the intervention, compared to the control group of infants. In a hospital-based RCT in Manila the efficacy of postnatal peer counselling was examined in a group of 204 term LBW infants (Level II evidence, see summary Table 5.1.1) (*325*). A total of 204 mothers were randomized into three groups; two intervention groups received home-based counselling visits (one by counsellors trained in breastfeeding counselling, the other by counsellors trained in general childcare), and a control group where the mothers did not receive counselling. No growth disadvantages were detected in the counselled group in this trial; all groups had improved mean weight-for-age standard deviation scores (z-scores) at 6 months, with no significant differences between the groups.

#### Effects on other important outcomes

One US RCT (Level II evidence, see summary Table 5.2.2) examined the impact of an intensive breastfeeding counselling package pre- and post-discharge to mothers of pre-term infants on the *mean duration of breastfeeding* (*326*). This package included individual counselling by a lactation consultant, weekly in-hospital contact, and frequent post-discharge contact. This was compared to standard breastfeeding support during the hospitalization period with no specialized lactation consultant available. In this study the mean breastfeeding duration increased from 24.2 weeks in the control group to 26.2 weeks in the intervention group, but the mean difference was not statistically significant. Exclusive breastfeeding at 1, 3, 6, and 12 months post-discharge was also not statistically different between the two groups. However, these results may be explained by the high motivation to breastfeed in both groups, a relatively advantaged population, and the availability of community breastfeeding resources, which may have diminished any significant differences that could have resulted

from a breastfeeding intervention. In contrast, the two RCTs described above detected significant improvements in EBF rates at 6 months (*187, 325*) (Table 5.2.2); breastfeeding counselling by skilled peers or professionals increased the breastfeeding rates in mothers of term infants (*327–329*), and case series of breastfeeding counselling interventions in developed countries reported increases in the incidence and mean duration of breastfeeding (*330–332*).

## Conclusions and implications

The findings of this section are based on the results of a number of RCTs in term, pre-term and SGA infants from developing and developed countries. A large effect of counselling on improving the rates of EBF in mothers of LBW infants was demonstrated with no apparent disadvantage in growth rates or malnutrition prevalence.

## Recommendations

No consensus statements or expert committee reports that examined the role of breastfeeding counselling in LBW infants were identified. Standard practice in many neonatal units is to provide breastfeeding counselling to mothers of LBW infants. The findings from this review support these recommendations.

**SUMMARY TABLE 5.2.1**
**Effect of breastfeeding counselling on growth outcomes in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| | | | | | | | Difference in proportions |
| Bhandari et al (*187*) Cluster RCT (LII) Subgroup analysis | Mothers of LBW infants (<2500 g at birth) | <1% | 15% | 85% | *Subgroup of LBW infants in:* Intervention group (community promotion of EBF for 6 mo) [n=159] *compared with* control group [n=124] | Height-for-age <–2 z-score | 9% [-2%, 20%] |
| | | | | | | Weight-for-height <–2 z- score | -2% [-6%, 1%] |
| Agrasada et al (*325*) RCT (LII) | Mothers of term LBW infants <2500 g who were admitted to hospital | None | None | 100% | Home-based breastfeeding counselling (n=60) *compared with* home- based counselling in general child care (n=59) | Weight-for-age z-score at 6 mo | MD -0.18 (-0.50, 0.14) |
| | | | | | Home-based in breastfeeding counselling (n=60) compared with no counselling at home (n=71) | Weight-for-age z-score at 6 mo | MD -0.18 (-0.48, 0.12) |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

**SUMMARY TABLE 5.2.2**
**Effects of breastfeeding counselling on breastfeeding patterns in LBW infants**

| Study, Design (Level of evidence) | Inclusion criteria | Approximate proportion of participants with gestation age[a] <32 wk | 32–36 wk | ≥37 wk | Comparison groups | Outcome measure | Effect measure [95% CI] |
|---|---|---|---|---|---|---|---|
| Pinelli et al (*326*) RCT (LII) | Parents of infants with birth weight <1500 g who intended to breastfeed | 100% | None | None | Breastfeeding counselling package (n=64) *compared with* standard package (n=64) | Mean duration of breastfeeding (weeks) | MD 2.10 [-5.12, 9.32] |
| Bhandari et al (*187*) Cluster RCT (LII) Subgroup analysis | Mothers of LBW infants (<2500 g at birth) | <1% | 15% | 85% | *Subgroup of LBW infants in:* Intervention group (community promotion of EBF for 6 mo) (n=159) *compared with* control group (n=124) | EBF at 3 months | RR 1.99 [1.58, 2.51] |
| | | | | | | EBF at 6 months | RR 9.67 [4.01, 23.3] |
| Agrasada et al (*325*) RCT (LII) | Mothers of term LBW infants <2500 g who were admitted to hospital | None | None | 100% | Home-based breastfeeding counselling (n=60) *compared with* home-based counselling in general child care (n=59) | EBF at 6 months | RR 6.39 [2.38, 17.2] |
| | | | | | Home-based in breastfeeding counselling (n=60) compared with no counselling at home (n=71) | EBF at 6 months | RR 26.4 [3.70, 188.7] |

[a] If gestational age was not available in the publication, infants with birth weight <1500 g are assumed to be <32 wk gestation, those weighing 1501–2000 g to be 32–36 wk gestation, and those weighing 2001–2500 g to have a gestation of 37 weeks or more.

## DRUG THERAPY

### Results

#### Effects on mortality rates, serious morbidity, neurodevelopment and malnutrition

No studies were located which examined the impact of lactogogues on mortality rates, serious morbidity, neurodevelopment and malnutrition in mothers of LBW infants.

#### Effects on other important outcomes

Three small studies from the US and Canada (Level III-3 evidence and above) evaluated the effects of metoclopramide or domperidone therapy on daily breastmilk volume in women who delivered infants <34 weeks gestation (*333–335*). In the comparative cohort study by Ehrenkranz et al, the women received metoclopramide 10 mg three times per day for 7 days (*333*). In contrast, de Silva et al randomized the women who were having difficulty maintaining milk production by milk expression to receive either domperidone or placebo for 7 days (*334*), while Hansen et al randomized women to receive either metoclopramide 10 mg or a placebo three times per day for 7 days (*335*). Ehrenkranz et al and de Silva et al reported large increases in milk production. In the study by Ehrenkranz et al, daily milk production doubled between the first and seventh day of therapy, which was associated with significantly increased basal serum prolactin levels (*333*). In the study by de Silva et al, milk volume also doubled in the intervention compared to the control group (*334*). However, Hansen et al reported no significant differences between breastmilk volumes in the metoclopramide and placebo groups on each of the 17 days of the study (*335*). Hansen et al also reported no significant difference between the groups in duration of breastfeeding, with a median of 8.8 weeks, an interquartile range of 3.4 to 12.0 weeks for the metoclopramide

group, and a median of 8.6 weeks and an interquartile range of 5.6 to 16.9 weeks for the placebo group (P = .09).

Other studies in mothers of term infants reported no effect of supplemental metoclopramide in women who received a package of counselling, motivation, support, and repeated suckling (*336*), while another study reported on the safety and efficacy of metclopramide therapy (*337*).

### Conclusions and implications

The findings of this section are based on three small trials which reported conflicting effects on increasing milk volume in mothers of infants under 34 weeks gestation, and one trial which reported no impact on the duration of breastfeeding. No information was presented on safety and no information was available concerning mothers of larger LBW infants.

### Recommendations

No consensus statements or expert committee reports which examined the role of lactogogues in LBW infants were identified. Standard practice in many neonatal units is to use metclopramide 10 mg three times per day as part of a package which includes counselling, support and education to improve lactation in mothers of LBW infants. It was not possible to provide additional recommendations due to insufficient evidence.

## BREASTMILK SUPPLEMENTER

A breastfeeding supplementer is a device for giving an infant a supplement while he is suckling at a breast which is not producing enough milk. A hungry infant may suckle at an 'empty' breast a few times, but he may become frustrated and refuse to suckle any more, especially if he has become used to sucking from a bottle. A breastfeeding supplementer helps to sustain the infant in suckling at the breast.

### Results

#### Effects on mortality, serious morbidity, neurodevelopment and malnutrition

No studies were located which examined the influence of breastfeeding supplementer on mortality, serious morbidity, neurodevelopment and malnutrition in LBW infants.

#### Effects on other important outcomes

Two case series were located which described the impact of the breastfeeding supplementer on *exclusive breastfeeding rates* (*337*, *338*). Both studies selected pre-term infants with birth weights <2500 g and showed that the supplementer could result in re-establishment of EBF. However, the methodological quality of the studies was poor, making it difficult to draw any conclusions.

### Conclusions and implications

The only studies located in this section were small case series that were likely to suffer from selection and observer bias, making it difficult to draw any conclusions.

### Current recommendations

No consensus statements or expert committee reports were located which examined the role of breastfeeding supplementer in LBW infants. Standard practice in many neonatal units is to use the breastfeeding supplementer with mothers who have difficulties in breastfeeding LBW infants. It was not possible to provide additional recommendations due to insufficient evidence.

# 6. MONITORING

Monitoring of LBW infants includes regular measurements of vital signs (i.e. temperature, heart rate, respiratory rate and blood pressure), oxygen saturation, gastric residual volumes, blood tests, and the monitoring of growth and neurodevelopment. In this section, blood glucose monitoring and growth monitoring are reviewed.

## 6.1 Blood glucose monitoring

### Results

#### Effects on mortality, serious morbidity and malnutrition

No studies were identified which examined the influence of blood glucose monitoring on mortality, serious morbidity and malnutrition in LBW infants.

#### Effects on neurodevelopment

Four studies (3 comparative cohort studies, 1 case series) were located which examined the impact of low blood glucose measurements on neurodevelopmental outcomes in LBW infants. Lucas et al compared the outcomes in a cohort of 661 UK infants with birth weights <1800 g (mean gestation 31 weeks, mean birth weight 1400 g) who were exposed and not exposed to 'moderate neonatal hypoglycaemia' (defined as plasma glucose concentration <2.6 mmol/l on ≥5 separate days) (*340*). Duvanel et al compared the outcomes in a cohort of 85 Swiss SGA infants (mean gestational age 32 weeks (range 27–34 weeks), mean birth weight 1200 g (range 580–1680 g) who were exposed and not exposed to 'moderate neonatal hypoglycaemia' (plasma glucose concentration <2.6 mmol/l on ≥5 separate days) (341). Pildes et al compared the outcomes in a cohort of 57 pre-term US infants with birth weights <2000 g (mean gestation 33 weeks, mean birth weight 1600 g) who were exposed and not exposed to 'moderate neonatal hypoglycaemia' (plasma glucose concentration <2.6 mmol/l on ≥5 separate days) (*342*). Brown et al described a case series of 15 infants of pre-term and SGA infants weighing <1500 g at birth with blood glucose levels of <1.1 mmol/l (*343*).

All four studies reported that blood glucose levels <2.6 mmol/l that occurred repeatedly were likely to be associated with poorer clinical outcomes in LBW infants. Lucas et al reported that frequent "moderate" hypoglycaemia (plasma glucose <2.6 mmol/l on at least 5 occasions) was strongly associated with abnormal neuromotor and intellectual performance at 18 months (*340*). Longer-term follow-up to 7½–8 years of age demonstrated persistent associations between moderate hypoglycaemia and developmental deficits in arithmetic and motor test scores after controlling for mother's education, social class and other important confounding factors, but the effect on the overall intelligence quotient was not significant (*344*). Duvanel et al reported that there was also an association between plasma glucose measurements of <2.6 mmol/l and developmental delay at 5 years of age (*341*). Pildes et al demonstrated that frequent "moderate" hypoglycaemia (plasma glucose <2.6 mmol/l) was associated with developmental deficit at the time of hospital discharge (*342*). Brown et al reported that 95% of the LBW infants in his case series with blood glucose levels <1.1 mmol/l had convulsions and abnormal neurological signs (*343*).

### Conclusions and implications

Studies in pre-term and term LBW infants indicate the need for avoiding prolonged and recurrent hypoglycaemia. However, no studies were found that examined the impact of such monitoring on improved survival, growth or neurodevelopment.

### Recommendations

Guidelines from WHO and other international groups recommend monitoring blood glucose in healthy LBW infants at 4-hourly intervals, each time before giving a feed, for the first 48 hours or until two measurements are >2.6 mmol/l and then daily until the infant is established on full enteral feeds (*345*). However, prevention by early enteral feeding (or provision of intravenous glucose for those unable to feed) is

more important than frequent blood glucose testing. Daily or twice daily laboratory measurements are preferable to frequent but inaccurate reagent strip measurements. They should be sufficient in most cases to tailor feeding regimens to the individual infant's requirement.

WHO recommendations also include treating symptomatic infants with blood glucose levels <2.6 mmol/l, monitoring asymptomatic infants with blood glucose levels <2.6 mmol/l closely, and treating asymptomatic LBW infants if the blood glucose level remains below this level or does not increase after a feed, or abnormal clinical signs develop (*345*). Others recommend close surveillance in term LBW infants if the plasma glucose concentration is <2.0 mmol/l and there are no symptoms (*346*). WHO and other international groups also recommend treating any asymptomatic LBW infants when the blood glucose concentration is <1.1 mmol/l (*346*, *347*). It is recommended that the decisions for treatment should be based on clinical signs and laboratory values and not on reagent strip values only.

## 6.2 Growth monitoring

### Results

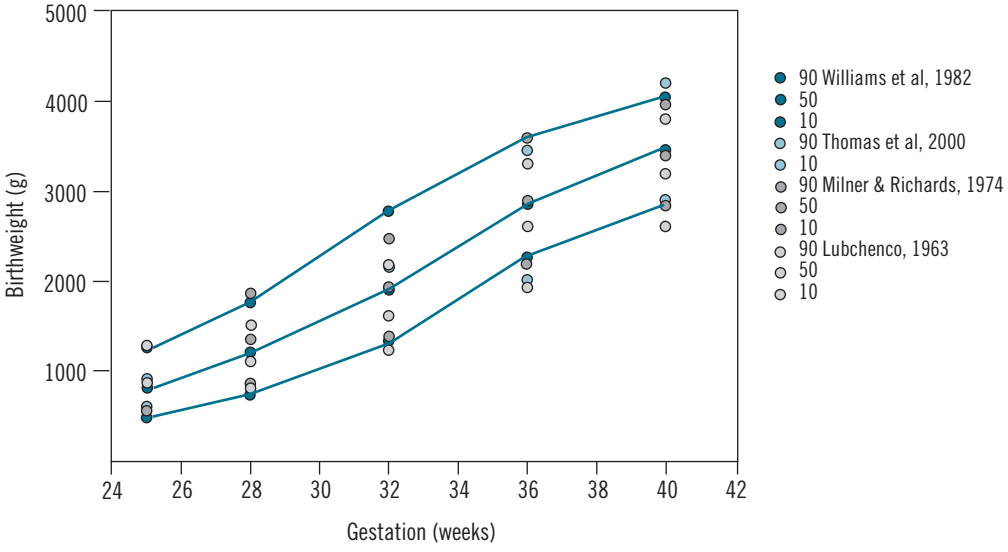
No studies were located which examined the impact of growth monitoring on mortality rates, serious clinical disease, neurodevelopment or growth in LBW infants.

### Intrauterine growth references

Many growth references such as the National Centres for Health Statistics (NCHS)/WHO chart do not provide data for pre-term infants (*347*, *348*). Several intrauterine growth references have been published for assessing size at birth according to gestational age. Some of these references for pre-term infants are summarized in Box 6.2.1.

Most of these were cross-sectional population-based studies reviewing routinely-collected hospital separation data, vital registration data and death certificates (*349*–*356*). There was one cross-sectional hospital-based study (*357*). WHO criteria were used to assess the pre-term anthropometric data sets and growth curves (Box 6.2.1) (*9*). No study fulfilled all of these criteria. Many of the references have problems, such as the cross-sectional nature of the data collection, rounding and inaccurate dating, selection bias (e.g. elective delivery for intrauterine growth failure), and secular change (e.g. change in infant feeding patterns and improvement in socio-economic status over time). This can cause significant misclassification of infants as SGA and LBW and growth faltering (*354*, *358*). The variability in four of these growth references is shown in Figure 6.2.1. The red lines represent the 90th, 50th and 10th centiles of the Williams 1982 reference (*9*).

**Figure 6.2.1** Comparison of growth references for preterm infants (from reference *359*)



**BOX 6.2.1 Reference data for size at birth** (Format adapted from reference 9)

| Location Author Year | Design | Sample size Duration of data collection | Representative-ness | Validity of gestational age | Ethnicity | Socio-economic status | Multiple births | Congenital malformations | Maternal pathologies and intrauterine infections | Quality of data source | Level of current use |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lubencho et al (*357*) Denver, USA | Cross sectional hospital based study reviewing hospital separation and admission data | 5,635 1948–1961 | Hospital based study of infants born at 24–42 weeks gestation | LMP | 70% Caucasian 30% Spanish, Mexican and Indian | Births included regardless of socio-economic status | Not discussed | Excluded gross pathological conditions which affected birth weight (anencephaly, hydrocephaly, hydrops fetalis, maternal diabetes) | Not discussed | Hospital separation and admission data | Wide |
| Milner and Richards (*349*) Multicentre, UK | Cross sectional population based based study reviewing hospital discharge data routinely collected by the Department of Health and Social Security | 271,519 1967–1971 | Hospital based study of infants born at 28–44 weeks gestation. | Not stated | Not stated | Births included regardless of socio-economic status | Excluded | Included | Included | Hospital discharge data | Appears to be limited |
| Brenner et al (*350*) Multicentre, US | Cross sectional population based study reviewing routinely collected hospital data | 31,268 1962–1975 | Large multicentre study of 30,772 liveborn infants delivered at 21–44 weeks gestation and 430 fetus aborted at 8–20 weeks gestation aborted with prosta-glandins | Best obstetric estimate and last normal menstrual period (LNMP) | Multiracial but groups not stated | Births included regardless of socio-economic status | Excluded | Excluded | Excluded | Routinely collected hospital data | Some sites |
| Williams et al (*351*) California, USA | Cross sectional population based study reviewing vital registration data | 2,288,806 1970–1976 | Population based Infants born at 22–44 weeks gestation | LMP and clinical estimation | Multiracial (9.9% Black, 25.8% Hispanic whites, 59.2% Non-Hispanic whites, 5.1% other) | Births included regardless of socio-economic status | Stratified | Included | Included | Birth registration certificate | Wide |

| Location Author Year | Design | Sample size Duration of data collection | Representative-ness | Validity of gestational age | Ethnicity | Socio-economic status | Multiple births | Congenital malformations | Maternal pathologies and intrauterine infections | Quality of data source | Level of current use |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Arbuckle et al (*352*) Multicentre, Canada | Cross sectional population based study reviewing vital statistics and health department birth registrations | 1,110,093 1986–1988 | Large multicentre study of vital registration data of infants born at > 22 weeks gestation | Not stated | Insufficient data provided | Births included regardless of socio-economic status | Stratified | Included | Included | Hospital vital registration data | Some sites |
| Freeman et al (*353*) 'UK90" chart Multicentre, UK | Pooled data from a number of multi-centre research studies of birth weight and subsequent growth | 13,312 (from birth to < 2 years of age) 1984–1994 | Hospital based studies of infants born at >22 weeks gestation | Early obstetric ultrasound | Whites only | Births included regardless of socio-economic status | Included | Included | Included | Prospective measurement by research staff | Through out UK |
| Alexander et al (*354*) Multisite, USA | Cross sectional population based study reviewing vital registration data | 3,134,879 1991 | Population based study of infants born at 22–44 weeks gestation | Early ultrasound measurement (majority) but also LMP | No information available | Births included regardless of socio-economic status | No | Included | No information | Birth registration certificate | Appears to be limited |
| Thomas et al (*355*) Multicentre, USA | Cross sectional population based study reviewing data inputted into database directly by health care provider | 27,729 1996–1998 | Hospital based study of infants born at >22 weeks gestation. Only infants who were admitted to the NICU were included. | Best estimate of the neonatologist based on obstetric history, obstetric examination, prenatal ultra-sound, and post-natal physical examination | 18,1% Black, 19.8% Hispanic, 2.5% Asian, 0.7% Native American, 58.9% White. | Births included regardless of socio-economic status | Included | Excluded | Included | Direct measurement and recording by hospital staff | Appears to be limited |
| Kramer et al (*356*) All provinces and territories of Canada excluding Ontario | Cross sectional population based study reviewing vital registration data | 676,605 1994–1996 | Population based Infants born at 22–43 weeks gestation | Early ultrasound measurement (majority) but also LMP | No information available | No information available | Singletons only | No information available | No information available | Linked file of live births and infant deaths | New reference |

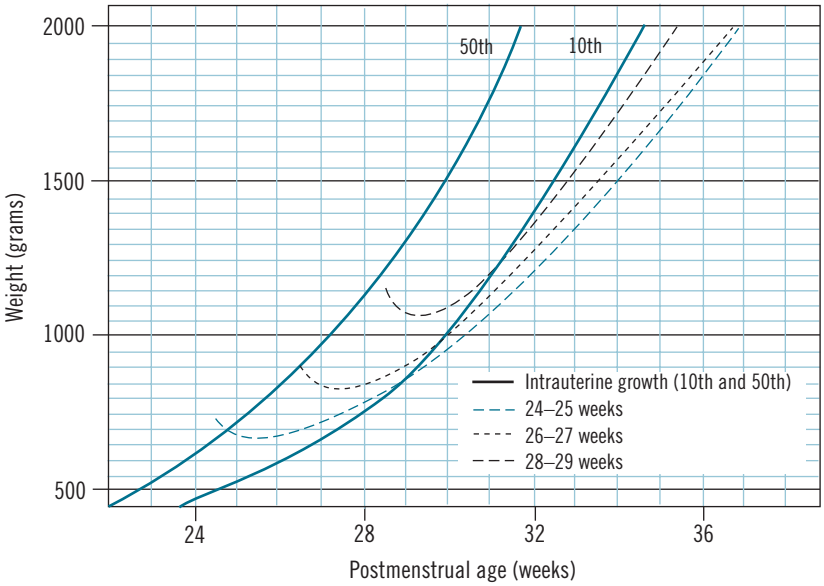
## Early postnatal growth references

Postnatal growth references from two prospective cohort studies of pre-term infants who received optimal nutritional management in neonatal care units in developed countries are summarized in Box 6.2.2 (*282*, *360*).

Postnatal growth curves of infants weighing 500–1500 g at birth in some neonatal care centres in the US show that infants at about the 50th centile for gestation lose about 10% of birth weight during the first week of life and regain birth weight by about 2 weeks of age, ending up at about the 10th centile of the intrauterine reference at this stage. Subsequent growth until term continues to diverge further from the 10th centile (see Figure 6.2.2) (*360*). Figure 6.2.2 has been drawn using a cross-sectional reference from 1996 which displays birth weight compared to gestational age (solid lines) (*354*). Longitudinal growth data from infants hospitalized in neonatal intensive care units in the US were used to draw the dashed lines (*360*).

The UK 1990 intrauterine growth reference chart provides a 9-centile format (Child Growth Foundation 1990) which allows the approximation of changes in growth in terms of z-score, each band width being 0.66SD. The lowest centiles on these charts are 2nd and 0.4th, which are very useful for plotting growth of babies <1500 g at birth. These charts should not be considered to be a prescriptive depiction of optimal growth but to be an indicator of a baby's position relative to a term-born counterpart.

**Figure 6.2.2** Average body weight versus postmenstrual age in weeks (From reference *360*)




**BOX 6.2.2 Reference data for postnatal growth with optimal nutritional management** (Format adapted from reference 9)

| Location Author Year | Design | Sample size Duration of data collection | Representativeness | Validity of gestational age | Ethnicity | Socio-economic status | Multiple births | Congenital malformations | Maternal pathologies and intrauterine infections | Quality of data source | Level of current use |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ehrenkranz et al (360), Multicentre, USA | Prospective hospital based study of live births with optimal nutritional management | 1660 1994–1995 | Hospital based study of Infants born at 500–1500 g birth weight | Best obstetric estimate or LMP | 35.6% White, 64.4% Non White. No other information | Births included regardless of socio-economic status | No information | Excluded | No information | Prospective measurement by hospital staff | New reference |
| Pauls et al (*282*) Berlin, Germany | **Prospective hospital based study of live births** with optimal nutritional management | 136 1991–1997 | **Hospital based study of Infants born at <1000 g** birth weight | **Best obstetric estimate or LMP** | **No information** | **Births included regardless of socio-economic status** | **Included** | **Included** | **Included** | **Prospective measurement by hospital staff** | **Appears to be limited** |

### Later postnatal growth of pre-term infants

Post-term growth in premature infants can be assessed using growth references created for term infants after correcting for gestation. Prior to 2006, the NCHS/WHO growth reference was commonly used (*347*). However, this reference was based on predominately formula-fed infants (*9, 361*) and many studies have demonstrated that breastfed infants grow less rapidly and deviate significantly from this reference (*9, 348, 361, 362*). A new international growth reference has been developed (*348*), which is based on predominately breastfed infants living in favourable socioeconomic conditions in six developing and developed countries (Brazil, Ghana, India, Norway, Oman, USA).

#### Conclusions and implications

No studies were located that studied the impact of growth monitoring in LBW infants on clinical outcomes.

Intrauterine growth can be assessed using references for size at birth such as the Williams 1982 or the UK 1990 references. Achieving a postnatal growth that approximates the *in utero* growth of a normal fetus at the same post-conception age is considered to be the logical approach by some experts. However, whether achieving fetal growth during postnatal life is optimum remains a hypothesis.

Early postnatal growth should be plotted against an intrauterine growth reference. However, it must be recognized that even in well-resourced neonatal care units in developed countries, exact mimicry of intrauterine growth in the postnatal period is not possible. Infants with birth weights <1500 g who are at the 50th centile of weight for gestation at birth lose about 10% of birth weight during the first week of life, regain the birth weight by about 2 weeks of age, and end up well below the 10th centile of the intrauterine reference by the time they reach term.

Postnatal growth after premature infants have reached term should be assessed using the new WHO Growth Reference. Corrected age should be used at least during the first year of life.

#### Recommendations

Standard practice is to weigh the LBW infant daily for the first week of life or until discharge from hospital, then twice a week or weekly until term, and then monthly until 12 months of chronological age. Babies who are unwell are weighed more frequently, especially if they are given IV fluids or if discharged early from the hospital, and particularly if the weight at discharge is <1500 g. Standard practice in many neonatal units is to plot early growth on an intrauterine growth reference chart. Many centres also use the Ehrenkranz postnatal growth reference to assess the adequacy of postnatal growth. Standard practice is also to use the WHO Road to Health charts from term to 12 months of chronological age. It was not possible to provide additional recommendations from this review.

## 7. FEEDING INFANTS OF HIV-POSITIVE MOTHERS

The risk of intrauterine and intrapartum mother-to-child transmission (MTCT) of HIV in term newborn infants, who were born to mothers who are known to be HIV-positive and who have not taken antiretroviral medication, has been described as 20–30% (*363, 364*). The risk of MTCT through human milk in term newborn infants, born to mothers who are known to be HIV-positive and who have not taken antiretroviral medication, is 10–15% (*363, 364*).

The risk of delivering a LBW infant is higher in HIV-positive women than in HIV-negative women (*365*). The risk of MTCT through human milk may be higher in LBW than non-LBW infants as the mother may have additional risk factors for transmission (e.g. a sexually transmitted infection, masti-

tis or cracked nipples). Among infants born to HIV-positive mothers, there is a twofold higher risk of becoming HIV-infected during intrapartum and early breastfeeding periods in pre-term infants than in infants born after 37 weeks (*366–368*). The risks of infection from replacement feeding are also likely to be higher in LBW than non-LBW infants as the former have a higher risk of impaired immunity and of infection (see sections 2.1 and 2.3). Thus, the balance of benefits and risks of breastfeeding in LBW infants may be similar to that in non-LBW infants.

HIV-infected mothers of LBW infants may not know their HIV status at the time of birth, especially if this is earlier than expected. Further, even if the mother knows her HIV status she may not have received HIV and infant feeding counselling.

We looked for published studies on the following issues:

- Choice of milk in infants born to HIV-positive mothers;
- Counselling on infant feeding for HIV-positive mothers of LBW infants.

## Results

### Effects on mortality, neurodevelopment and malnutrition

No studies were located which examined the impact of choice of milk or counselling on HIV and infant feeding on mortality rates, severe morbidity, neurodevelopment and malnutrition/growth in LBW infants born to HIV-positive mothers.

### Effects on serious morbidity – HIV transmission

There is evidence from observational studies in South Africa that the risk of HIV transmission is lower if infants are exclusively breastfed (EBF), compared with mixed feeding, in the first months of life (*367*). A recent study from Zimbabwe supports this observation (*369*). HIV transmission rates/100 child-years at 6 months were 5.1 for exclusive breastfeeding, 6.7 for predominant breastfeeding, and 10.5 for mixed feeding. However, some studies have questioned a causal link and have provided data suggesting the potential for reverse causality, i.e. infants who are HIV-positive and unwell are more likely not to be exclusively breastfed (*370*). There are no data on the risks of HIV transmission in infants who moved from formula/mixed feeding to EBF early in life.

No data were located that examined the impacts of heat treatment of mother's own milk in HIV-positive mothers of LBW infants. In non-LBW infants, heat treatment by flash and Pretoria pasteurization methods inactivates HIV (*76–79*). Both methods have been shown to reduce HIV-1 by >3 logs and eliminate bacterial contaminants, while flash treatment resulted in undetectable reverse transcriptase activity (*76–79*). Neither method was reported to cause significant decrease in any vitamin, lactoferrin or lysozyme. These methods could be implemented by a mother in a developing country, but studies have shown that acceptability is variable (*371, 372*).

## Recommendations

The current UN recommendations on feeding infants of HIV-positive women are replacement feeding when this is acceptable, feasible, affordable, sustainable and safe, or EBF for the first few months of life and cessation of breastfeeding as early as possible. There is no difference in the recommendations for normal and LBW infants. It was not possible to provide additional recommendations due to insufficient evidence.

ANNEX 1

# Definitions

**Low birth weight infant (LBW)** = infant with birth weight less than 2500 g.

**Very low birth weight infant (VLBW)** = infant with birth weight less than 1500 g.

**Pre-term infant** = infant born before 37 weeks of gestational age.

**Term infant** = infant born between 37 and 42 weeks of gestational age.

**Pre-term birth** = birth occurring before 37 weeks of gestational age.

**Term birth** = birth occurring between 37 and 42 weeks of gestational age.

**Post-term birth** = birth occurring after 42 weeks of gestational age.

**Small for gestational age (SGA)** = an infant whose birth weight is less than the 10th centile for gestational age at birth.

**Appropriate for gestational age (AGA)** = an infant whose birth weight is between the 10th centile and the 90th centile for gestational age at birth.

**Corrected age (i.e. corrected for prematurity)** = the age of the infant in weeks from the date of birth minus the number of weeks that the infant was born early.

**Chronological age** = the age of the infant in weeks from the date of birth without correcting for prematurity.

**Transition period** = the period from birth to 7 days when infants are likely to be clinically and metabolically unstable and to lose weight.

**Stable growing period** = the period beginning when the infant is metabolically and clinically stable and ending when the infant reaches 37 weeks of post-conception age.

**Kangaroo mother care (KMC)** = early continuous and prolonged skin-to-skin contact between the mother and infant combined with exclusive breastfeeding.

**Standard infant formula** = formula designed for term infants, based on the composition of mature breastmilk. The typical energy content is 68 kcal/100ml. The concentration of protein is approximately 1.5 g/100ml and the calcium and phosphorus content 50 mg/100ml and 30 mg/100ml respectively.

**Pre-term infant formula** = formula especially designed for premature infants. Pre-term formulas are enriched in calories (approximately 80 kcal/100ml) and variably in protein and minerals to support intra-uterine nutrient accretion rates. The calories may be provided as protein, fat or carbohydrate and the balance between calories and protein may be critical in determining the type of growth. Compared to unsupplemented human milk or 'standard infant formula', pre-term formulas contain more protein, sodium, calcium, phosphorus, zinc, copper and vitamins, often in a form that is more easily absorbed and metabolised. Most have an energy content of about 80 kcal/100ml. In spite of the higher carbohydrate and mineral content, the osmolality of 'pre-term formulas' remains low at around 250–320 mOsm/kg $H_2O$. 'Pre-term formulas' also contain at least 2 g/100ml of protein so that the premature infant will receive 3 g/kg/d of protein when fed at 150 ml/kg/day.

**Nutrient-enriched post-discharge formula** = formula especially designed for LBW infants after they have reached term gestational age. 'Post-discharge formulas' are intermediate in composition between 'pre-term' and 'term' formulas. Compared to unsupplemented human milk or 'standard infant formula', 'post-discharge formulas' contain more protein, sodium, calcium, phospho-

rus, zinc, copper and vitamins, often in a form that is easily absorbed and metabolised. Most have an energy content of about 70 kcal/100ml (22 kcal/oz). In spite of the higher carbohydrate and mineral content, the osmolality of 'post-discharge formula' remains low at around 250–320 mOsm/kg $H_2O$. 'Post-discharge formulas' also contain at least 2 g/100ml of protein so that the infant will receive 3 g/kg/d of protein when fed at 150 ml/kg/day.

**Enteral feeding** = administration of any feed into the gastrointestinal tract; it includes intragastric feeding and cup, bottle and breastfeeding.

**Early initiation of 'maintenance' enteral feeds** = enteral feeding of at least 40 ml/kg/day for the first 24 hours of life

**Trophic feeding or minimal enteral nutrition** = any enteral milk feed in the first 24 hours of life in sub-nutritional quantities (e.g. 5–10 ml/kg/day on the first day) (also called "minimal enteral feeding", "gut priming", and "early hypo-caloric feeding").

**Bolus feeding** = a calculated amount of fluid, given intermittently, every 1–4 hours depending on weight and gestational age.

**Oral feeding** = administration of any feed into the oral cavity; it includes cup, paladai, spoon, syringe, direct expression, bottle and breastfeeding but not gastric tube feeding.

**Paladai** = a traditional feeding device used in some South Indian communities. It is shaped like a small cup (30 ml capacity) with an open spout for pouring the milk gently into the infant's mouth.

**Rooting** = the response of a baby when the side of the cheek is touched, which makes him turn to the breast with the mouth wide open

**Feasibility** = the practicability of implementing an intervention in a first referral healthcare facility in a developing country.

**Catch-up growth** = any improvement in centiles or z scores. Early catch-up is defined as fast growth in infancy among small newborns and late catch-up is defined as improvement in growth from 1 year of age until adulthood.

**Metabolic bone disease or osteopenia of prematurity** = characteristic osteopenic radiological appearance, a low bone mineral content or peak alkaline phosphatase of >1200 IU.

**Stable infant** = an infant whose vital functions (particularly the respiration and heart rate) are not subject to rapid and unexpected worsening, regardless of intercurrent disease, and do not depend on continuous medical monitoring and support (e.g. use of a mechanical ventilator).

**Unstable infant** = an infant who has danger signs and is subject to rapid and unexpected worsening, whose vital functions depend on continuous medical monitoring and support.

**Exclusive breastfeeding (EBF)** = breastfeeding with no supplemental liquid or solid foods other than medications or vitamins.

**Predominant breastfeeding** = breastfeeding plus water-based fluids (e.g. water, juice or tea) but no solids, milks or gruels.

**Partial breastfeeding** = breastfeeding plus water-based fluids, solids, milks or gruels.

**Non-breastfed** = no breastmilk given.

ANNEX 2

# Levels of evidence

Levels of evidence were rated according to the following scale (US Preventative Services Task Force 1989).

I. Evidence obtained from a systematic review of all relevant randomized controlled trials

II Evidence obtained from at least one properly designed randomized controlled trial

III-1 Evidence obtained from well-designed pseudo-randomized controlled trials (alternate allocation or some other method)

III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies), case control studies, or interrupted time series with a control group

III-3 Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group

IV Evidence obtained from case series, either post-test or pre-test and post-test

ANNEX 3

# Sources and quality of evidence

| TOPIC | SOURCES AND QUALITY OF EVIDENCE |
|---|---|
| **NUTRITION** | |
| **Breastfeeding or mother's own expressed milk** | Three of the five studies that examined the effects on infection were observational. One of the three observational studies did not adjust for confounding. A meta-analysis of cohort studies, which adjusted for appropriate confounders, was the basis of findings related to neurodevelopment. In most studies, comparison group was infants fed standard infant formula. |
| **Donor human milk** | The findings are based on 5 RCTs and their meta-analyses. The trials were small and unblinded. Most of these studies used donor drip milk, which is predominantly fore milk. Further, most studies were initiated over 20 years ago and used standard infant formula milk as the comparison. |
| **Optimal duration of exclusive breastfeeding** | There are limited data available. The 3 RCTs identified did not measure effect of EBF duration on mortality and morbidity and only one trial reported effects on neurodevelopment. The sample sizes of two of these studies were small. Contrary to other issues, most studies were conducted in term, SGA infants. |
| **Human milk supplementation with multicomponent fortifier** | Findings are largely based on RCTs and their meta-analysis. The studies examining the effects on mortality and necrotising enterocolitis were too small to get precise estimates. There was a large amount of missing data in the studies |
| **Human milk supplementation with single nutrients** | **Vitamin A** There are no data examining the effect of usually recommended dose of 700–1500 IU/kg body weight daily. Three RCTs (2 small, one with adequate sample size) examined the mortality effect of a large dose (50,000 IU in one or two divided doses) of vitamin A during the first days of life. |
| | **Vitamin D** The findings are from case series and a single RCT that compared a high dose of vitamin D (2000 IU per day) with the usual dose of 400 IU per day. |
| | **Calcium and phosphorus** The findings are based on two small RCTs. |
| | **Iron** The findings are based on observational studies examining iron status of breastfed LBW infants and two RCTs that examined effects of iron supplementation on iron status in LBW infants. |
| | **Zinc** Findings are based on RCTs. Most of these RCTs had smaller than appropriate sample sizes. |

| TOPIC | SOURCES AND QUALITY OF EVIDENCE |
|---|---|
| **Pre-term vs. standard infant formula** | The findings are largely based on one large, well designed RCT comparing pre-term infant formula with standard term infant formula in pre-term infants. 80% of study participants were <1500 g at birth. |
| **Nutrient-enriched post-discharge formula vs. standard formula** | The findings are largely based on 3 RCTs examining the effect of nutrient-enriched post-discharge formula compared with standard formula on neurodevelopment and growth. There are no data for other outcomes |
| **FEEDING METHODS** | |
| **Cup feeding vs. bottle feeding** | None of the available studies examined the effects of different oral feeding methods on key clinical outcomes. Two RCTs and 6 observational studies examined the effect of cup feeding compared to bottle feeding on breastfeeding rates at hospital discharge. One study compared cup, 'paladai' and bottle feeding. Most studies were of poor quality and longer-term outcomes (post hospital discharge) were not assessed. |
| **Use of nasogastric vs. orogastric tubes** | Only one small descriptive study was located. |
| **Bolus vs. continuous feeding** | The findings are based on meta-analyses of RCTs or large RCTS performed in developed country infants <1500 g at birth. The studies had small sample sizes and inconsistencies in controlling variables that affect outcomes. |
| **FEEDING SCHEDULES** | |
| **Trophic feeding or minimal enteral nutrition** | A systematic review and meta-analysis of 10 RCTs was located. The trials were of intermediate methodological quality. Many studies did not mention how randomization was concealed, did not attempt blind assessments and did not include results for all infants randomized. |
| **Initiation of 'maintenance' enteral feeding** | No studies examined the role of early initiation of breastfeeding in LBW infants. The only available studies were from the 1960s which examined impacts of nasogastric feeding on day 1 in pre-term infants. All had design flaws and two of the 4 studies did not provide results stratified by birth weight or gestation. |
| **Progression of enteral feeding** | The findings are based on meta-analyses of RCTs from developed countries. The studies included in the meta-analyses were heterogeneous and subject to observer and diagnostic surveillance bias. |
| **Volume of enteral feeds in the second week of life** | Only 1 small RCT was located which compared the administration of different daily fluid volumes in the second week of life in infants who were <30 weeks gestation at birth. |

| TOPIC | SOURCES AND QUALITY OF EVIDENCE |
|---|---|
| **Feed frequencies and intervals** | Only case series and descriptive studies were located in this section. However, no comparative studies were available to allow decisions to be made about the safest or most effective regimes. No implications can be drawn for infants of particular gestational ages or birth weights. |
| **Demand or scheduled feeding** | Only 1 small study was located which examined impacts of demand feeding of pre-term infants by the time they had reached 1800 g. |
| **SUPPORT** | |
| **Kangaroo mother care** | The 3 available RCTs only included stabilized LBW infants. The studies were of moderate to poor methodological quality (unblinded, large proportion of drop-outs and loss to follow-up). One RCT and two observational studies which examined the effects of KMC in un-stabilized LBW infants were identified |
| **Non-nutritive sucking** | Findings are based on a meta-analysis of 3 small RCTs. Results are difficult to interpret due to small sample sizes and other methodological flaws. An intervention study that examined the effect of sucking on 'emptied breast' was also identified |
| **Early discharge from hospital** | Eight RCTs in infants <2000 g were located which examined the effect of early discharge of low birth weight infants after they were clinically stable, on full oral feeds and mother demonstrated satisfactory care-taking skills. |
| **Involvement of mothers in care and feeding of their LBW infants** | Three studies were located which described the effects of maternal participation in care of their LBW infants |
| **Breastfeeding counselling** | The findings are based on results of two RCTs in pre-term and SGA infants. One was a small study in infants <1500 g and the other was a subgroup analysis of a community-based intervention trial of EBF promotion. |
| **Drug therapy** | The findings of this section are based on 2 small trials in mothers of infants <32 weeks gestation, but no information on safety is available. No information was available in mothers of larger LBW infants. |
| **MONITORING** | |
| **Blood glucose monitoring** | No studies were found that examined the impact of such monitoring on improved survival, growth or neurodevelopment. Four observational studies were located that examined the association of low blood glucose with subsequent outcomes. |
| **Growth monitoring** | No studies were located which examined the impact of growth monitoring on key clinical outcomes. |
| **HIV AND INFANT FEEDING** | |
| | No studies were located which examined the impact of HIV and infant feeding counselling of HIV-positive mothers of LBW infants or the choice of milk on key clinical outcomes. |

ANNEX 4

# References


1. WHO & UNICEF. *Low birthweight: Country, regional and global estimates*. Geneva, United Nations Children's Fund and World Health Organization, 2004.
2. Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? *Lancet*, 2005, 365(9462):891–900.
3. Ashworth A. Effects of intrauterine growth retardation on mortality and morbidity in infants and young children. *European Journal of Clinical Nutrition*, 1998, 52 Supplement 1:S34–41.
4. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *New England Journal of Medicine*, 1985, 312:82–90.
5. Fryer JG, Ashford JR. Trends in perinatal and neonatal mortality in England and Wales 1960–69. *British Journal of Preventive and Social Medicine*, 1972, 26(1):1–9.
6. Bang AT et al. Low birth weight and preterm neonates: can they be managed at home by mother and a trained village health worker? *Journal of Perinatology*, 2005, 25 Supplement 1:S72–81.
7. Daga SR et al. Anganwadi worker's participation in rural newborn care. *Indian Journal of Pediatrics*, 1993, 60(5):627–30.
8. Pratinidhi AK et al. Domiciliary care of low birth weight neonates. *Indian Journal of Pediatrics*, 1986, 53(1):87–92.
9. WHO 1995. Expert Committee on the Use and Interpretation of Anthropometry. *Physical Status: The Use and Interpretation of Anthropometry*. Geneva, World Health Organization, 1995.
10. Hales CN. Metabolic consequences of intrauterine growth retardation. *Acta Paediatrica Scandinavica* supplement, 1997, 423:184–187.
11. American Academy of Pediatrics Committee on Fetus and Newborn. Hospital discharge of the high risk neonate: proposed guidelines. *Pediatrics*, 1998, 102:411–417.
12. Klaus MH, Fanaroff AA, eds. *Care of the high risk neonate*, 5th ed. Philadelphia, Saunders, 1999.
13. de Onis M, Blossner M, Villar J. Levels and patterns of intrauterine growth retardation in developing countries. *European Journal of Clinical Nutrition*, 1998, 52 Supplement 1:S5–15.
14. Kramer MS. Socioeconomic determinants of intrauterine growth retardation. *European Journal of Clinical Nutrition*, 1998, 52 Supplement 1: S29–32.
15. Ashworth A, Morris SS, Lira PI. Postnatal growth patterns of full-term low birth weight infants in Northeast Brazil are related to socioeconomic status. *Journal of Nutrition*, 1997, 127:1950–6.
16. Lucas A et al. A randomized multicentre study of human milk versus formula and later development in preterm infants. *Archives of Disease in Childhood: Fetal and Neonatal edition* (supplement), 1994, 70:F141–F146.
17. Lucas A et al. Randomized outcome trial of human milk fortification and developmental outcome in preterm infants. *American Journal of Clinical Nutrition*, 1996, 64:142–151.
18. Henderson G, Anthony MY, McGuire W. Formula milk versus term human milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2001, Issue 4. Art. No.: CD002971. DOI: 10.1002/14651858.CD002971.
19. Victora CG et al. Short-term benefits of catch-up growth for small-for-gestational-age infants. *International Journal of Epidemiology*, 2001, 30(6): 1325–30.
20. Stein CE et al. Fetal growth and coronary heart disease in south India. *Lancet*, 1996, 348(9037): 1269–73.
21. Rich-Edwards JW et al. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *British Medical Journal*, 1997, 315(7105):396–400.
22. Leon DA et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915–29. *British Medical Journal*, 1998, 317(7153):241–5.
23. Forsen T et al. The fetal and childhood growth of persons who develop type 2 diabetes. *Annals of Internal Medicine*, 2000, 133(3):176–82.

24. Singhal A, Cole TJ, Lucas A. Early nutrition and later blood pressure: two cohorts after randomized trials. *Lancet*, 2001, 357:413–9.

25. Singhal A et al. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. *Lancet*, 2003, 361:1089–97.

26. Frankel S et al. Birthweight, body–mass index in middle age, and incident coronary heart disease. *Lancet*, 1996, 348:1478–80.

27. Eriksson JG et al. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *British Medical Journal*, 1999, 318:427–431.

28. Eriksson JG et al. Early growth and coronary heart disease in later life: a longitudinal study. *British Medical Journal*, 2001, i:949–53.

29. Barker DJ et al. Trajectories of growth among children who have coronary events as adults. *New England Journal of Medicine*, 2005, 353(17):1802–9.

30. Bhargava SK et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. *New England Journal of Medicine*, 2004, 350(9):865–75.

31. Ziegler EE, Ryu JE. Renal solute load and diet in growing premature infants. *Journal of Pediatrics*, 1976, 89(4):609–11.

32. Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics*, 1961, 28:169–81.

33. Fusch, F. Jochum. Water, sodium, potassium, and chloride. In: Tsang RC et al, eds. *Nutrition of the preterm infant: scientific basis and practical guidelines*, 2nd ed. Cincinnati, OH, Digital Educational Publishing, 2005.

34. Bell EF, Oh W. Fluid and electrolyte management. In: Avery GB, Fletcher MA, MacDonald MG , eds. *Neonatology: Pathophysiology of the Newborn*, 5th ed. Philadelphia Lippincott Williams and Wilkins, 1999:345–61.

35. Fomon SJ et al. Body composition of reference children from birth to age 10 years. *American Journal of Clinical Nutrition*, 1982, 35:1169–1175.

36. Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 2001, Issue 3. Art. No.: CD000503. DOI: 10.1002/14651858.CD000503.

37. Grunhagen DJ et al. Transepidermal water loss during halogen spotlight phototherapy in preterm infants. *Pediatric Research*, 2002, 51(3):402–5.

38. Maayan-Metzger A et al. Effect of radiant warmer on transepidermal water loss (TEWL) and skin hydration in preterm infants. *Journal of Perinatology*, 2004, 24(6):372–5.

39. Leitch, Denne. Energy. In: Tsang RC et al, eds. *Nutrition of the preterm infant: scientific basis and practical guidelines*, 2nd ed. Cincinnati, OH, Digital Educational Publishing, 2005.

40. Williams AF. Human milk and the preterm infant. In: Hansen TN, McIntosh N, eds. *Current topics in neonatology*. London, WB Saunders, 1999, 3:43–61.

41. Senterre J, Rigo J. Protein requirements of premature and compromised infants. In: Xanthou M, ed. *New aspects of nutrition in pregnancy, infancy and prematurity*, Amsterdam: Elsevier, 1997:109–115.

42. Fomon SJ, Ziegler EE. Renal solute load and potential renal solute load in infancy. *Journal of Pediatrics*, 1999, 134(1):11–4.

43. Canadian Paediatric Society Nutrition Committee. Nutrient needs and feeding of premature infants. *Canadian Medical Association Journal*, 1995, 152:1765–1785.

44. American Academy of Pediatrics Committee on Nutrition. Nutritional needs for low-birth-weight infants. *Pediatrics*, 1985, 75: 976–986.

45. European Society of Paediatric Gastroenterology and Nutrition. Committee on Nutrition of the Preterm Infant, Nutrition and feeding of preterm infants. *Acta Paediatrica Scandinavica* supplement, 1987, 336: 1–14

46. Schanler R. Human milk. In: Tsang RC et al, eds. *Nutrition of the preterm infant: scientific basis and practical guidelines*, 2nd ed. Cincinnati, OH, Digital Educational Publishing, 2005.

47. May JT. Antimicrobial factors and microbial contaminants in human milk: recent studies. *Journal of Paediatrics and Child Health*, 1994, 30:470–475.

48. Avery GB, Fletcher MA. *Neonatology: pathophysiology and management of the newborn*. New York; London: Lippincott, Williams & Wilkins, 2005.

49. Friel JK et al. Elemental composition of human milk from mothers of premature and full-tern infants during the first 3 months of lactation. *Biological Trace Element Research*, 1999, 67:225–247.

50. Thorell L et al. Nucleotides in human milk: sources and metabolism by the newborn infant. *Pediatric Research* 1996;40:845–852.

51. Balmer SE, Hanvery LS, Wharton BA. Diet and faecal flora in the newborn: nucleotides. *Archives of Disease in Childhood Fetal and Neonatal Edition*, 1994, 70:F137–F140.

52. Brunser O et al. Effect of dietary nucleotide supplementation on diarrhoeal disease in infants. *Acta Paediatrica*, 1994, 83:188–191.

53. Carver JD, Barness LA. Trophic factors for the gastrointestinal tract. *Clinics in Perinatology*, 1996, 23:265–285.

54. Carlson SE et al. Lower incidence of necrotizing enterocolitis in infants fed a preterm formula with egg phospholipids. *Pediatric Research*, 1998, 44:491–498.

55. Kurlak LO, Stephenson TJ. Plausible explanations for effects of long chain polyunsaturated fatty acids (LCPUFA) on neonates. *Archives of Disease in Childhood Fetal and Neonatal Edition*, 1999, 80: F148–F154.

56. Rueda R et al. Neonatal dietary gangliosides. *Early Human Development*, 1998, 53(Supplement): S135–S147.

57. Pan XL, Izumi T. Variation of the ganglioside compositions of human milk, cow's milk and infant formulas. *Early Human Development*, 2000, 57:25–31.

58. United Kingdom Association for Milk Banking. *Guidelines for the Establishment and Operation of Human Banks in the UK*, 3rd ed. London: Royal College of Paediatrics and Child Health and United Kingdom Association for Milk Banking, 2004.

59. Human Milk Banking Association of North America. *Guidelines for Establishment and Operation of a Donor Human Milk Bank*. Raleigh, NC: Human Milk Banking Association of North America Inc; 2003.

60. Valentine CJ, Hurst NM, Schanler RJ. Hindmilk improves weight gain in low-birth-weight infants fed human milk. *Journal of Pediatric Gastroenterology and Nutrition*, 1994, 18:474–7.

61. Slusher T et al. Promoting the exclusive feeding of own mother's milk through the use of hindmilk and increased mother's own milk volume for hospitalized, low birth weight infants (< 1800 grams) in Nigeria: a feasibility study. *Journal of Human Lactation*, 2003, 19(2):191–8.

62. Lucas A, Gibbs JA, Baum JD. The biology of human drip breast milk. *Early Human Development*, 1978, 2(4):351–61.

63. Gibbs JH et al. Drip breast milk: its composition, collection and pasteurisation. *Early Human Development*, 1977, 1(3): 227–245.

64. Lang S, Lawrence CJ, Orme BL. Sodium in hand and pump expressed human breastmilk. *Early Human Development* 1994; 38: 131–8.

65. Liebhaber M et al. Comparison of bacterial contamination with two methods of human milk collection. *Journal of Pediatrics*, 1978, 92:236–237.

66. Tyson JE et al. Collection methods and contamination of bank milk. *Archives of Disease in Childhood*, 1982, 57:396–8.

67. Boo NY et al. Contamination of breastmilk obtained by manual expression and breast pumps in mothers of very low birth weight infants. *Journal of Hospital Infection*, 2001, 49:274–281.

68. WHO and UNICEF. B*reastfeeding counselling: A training course*. Geneva, World Health Organization, 1992 (WHO/CDR/93.5/UNICEF/NUT/93.5).

69. Wills ME, Han VEM, Harris DA. Short time low temperature pasteurisation of human milk. *Early Human Development*, 1982, 7:71–80.

70. Eglin RP, Wilkinson AR. HIV infection and pasteurisation of breast milk. *Lancet*, 1987, i:1093.

71. Orloff SL, Wallingford J , McDougall JS. Inactivation of Human Immunodeficiency Virus Type I in human milk: effects of intrinsic factors in human milk and pasteurisation. *Journal of Human Lactation*, 1993, 9:13–17

72. van Zoeren-Grobben D et al. Human milk vitamin content after pasteurisation, storage or tube feeding. *Archives of Disease in Childhood*, 1987, 62:161–165.

73. Williamson S et al. Effect of heat treatment of human milk on absorption of nitrogen, fat, sodium, calcium and phosphorus by preterm infants. *Archives of Disease in Childhood*, 1978, 53:555–563.

74. Paxson CL, Cress CC. Survival of human milk leukocytes. *Journal of Pediatrics*, 1979, 94:61–64.

75. Liebhaber M et al. Alterations of lymphocytes and of antibody content of human milk after processing. *Journal of Pediatrics*, 1977;91:897–900.

76. Israel-Ballard K et al. Acceptability of heat treating breast milk to prevent mother-to-child transmission of human immunodeficiency virus in Zimbabwe: a qualitative study. *Journal of Human Lactation*, 2006, 22(1):48–60.

77. Jeffrey BS, Mercer KG. Pretoria pasteurisation: a potential method for the reduction of postnatal mother to child transmission of the human immunodeficiency virus. *Journal of Tropical Pediatrics*, 2000, 46:219–223.

78. Jeffrey BS, Webber L, Mokhondo KR. Determination of the effectiveness of in activation of human immunodeficiency virus by Pretoria pasteurisation. *Journal of Tropical Pediatrics*, 2001, 47:345–9.

79. Chantry CJ, Morrision P. Panchula J. Effects of lipolysis or heat treatment on HIV-1 provirus in breast milk. *Journal of Acquired Immune Deficiency Syndrome*, 2000, 24:325–9.

80. Pittard WB 3rd et al. Bacteriostatic qualities of human milk. *Journal of Pediatrics*, 1985, 107:240–243.

81. Nwankwo MU et al. Bacterial growth in expressed breastmilk. *Annals of Tropical Paediatrics*, 1988, 8: 92–95.

82. Sosa R, Barness L. Bacterial growth in refrigerated human milk. *American Journal of Diseases of Children*, 1987, 141:111–112

83. Larson E et al. Storage of human breastmilk. *Infection Control*, 1984, 5: 127–130.

84. Pardou A et al. Human milk banking: influence of storage processes and of bacterial contamination on some milk components. *Biology of the Neonate*, 1994; 65: 302–9.

85. Ford JE et al. Influence of heat-treatment of human milk on some of its protective constituents. *Journal of Paediatrics*, 1977, 90:29–35.

86. Moffatt PA et al. a- and g-tocopherols in pooled mature human milk after storage. *Journal of Pediatric Gastroenterology and Nutrition*, 1987, 6:225–7.

87. Vidal-Valverde C, Ruiz R, Medrano A. Stability of retinol in milk during frozen and other storage conditions. *Zeitschrift für Lebensmittel-Untersuchung und-Forschung*, 1992, 195: 562–5.

88. Garza C et al. Effects of methods of collection and storage on nutrients in human milk. *Early Human Development*, 1982, 6:295–303

89. Evans TJ et al. Effect of storage and heat on antimicrobial proteins in human milk. *Archives of Disease in Childhood*, 1978, 53:239–241

90. Sigman M et al. Effects of microwaving human milk: changes in IgA content and bacterial count. *Journal of the American Dietetic Association*, 1989, 89(5):690–2.

91. Ovesen L et al. The effect of microwave heating on vitamins B1 and E, and linoleic and linolenic acids, and immunoglobulins in human milk. *International Journal of Food Sciences and Nutrition*, 1996, 47(5):427–36.

92. Quan R et al. Effects of microwave radiation on anti-infective factors in human milk. *Pediatrics*, 1992, 89(4 Pt 1):667–9.

93. Friis H, Andersen HK. Rate of inactivation of cytomegalovirus in raw banked milk during storage at -20 degrees C and pasteurisation. *British Medical Journal Clinical Research Edition*, 1982, 285(6355):1604–5.

94. Hamprecht K et al. Cytomegalovirus (CMV) inactivation in breast milk: reassessment of pasteurization and freeze-thawing. *Pediatric Research*, 2004, 56(4):529–35.

95. Forsgren M. Cytomegalovirus in breast milk: reassessment of pasteurization and freeze-thawing. *Pediatric Research*, 2004, 56(4):526–8.

96. Moyer-Mileur L, Chan GM, Gill G. Evaluation of liquid or powdered fortification of human milk growth and bone mineralization status of preterm infants. *Journal of Pediatric Gastroenterology and Nutrition*, 1992, 15:370–374.

97. Narayanan I. Nutrition for preterm and growth retarded infants: developing country concerns. *Human Nutrition Applied Nutrition*, 1985, 39(4): 242–54.

98. Suryavanshi N et al. Infant feeding practices of HIV-positive mothers in India. *Journal of Nutrition*, 2003, 133(5):1326–31.

99. Phadke MA et al. Replacement-fed infants born to HIV-infected mothers in India have a high early postpartum rate of hospitalization. *Journal of Nutrition*, 2003, 133(10):3153–7.

100. Papathakis PC, Rollins NC. Are WHO/UNAIDS/UNICEF-recommended replacement milks for infants of HIV-infected mothers appropriate in the South African context? *Bulletin of the World Health Organization*, 2004, 82(3):164–71.

101. Kashyap S et al. Protein quality in feeding low birth weight infants: a comparison of whey-predominant versus casein-predominant formulas. *Pediatrics*, 1987;79:748–755

102. Kuschel CA, Harding JE. Protein supplementation of human milk for promoting growth in preterm infants. *Cochrane Database of Systematic Reviews*, 2000, Issue 2. Art. No.: CD000433. DOI: 10.1002/14651858.CD000433.

103. Davidson M et al. Feeding studies in low birth weight infants. I. Relationships of dietary protein, fat and electrolyte to rates of weight gain, clinical courses and serum chemical concentrations. *Journal of Pediatrics*, 1967, 70:695–713.

104. Goldman HI et al. Late effects of early dietary protein intake on low birth weight infants. *Journal of Pediatrics*, 1974, 85:764–769

105. Huston RK et al. Nutrient and mineral retention and vitamin D absorption in low birth weight infants: effect of medium-chain triglycerides. *Pediatrics*, 1983, 72:44–48.

106. Centers for Disease Control and Prevention. Enterobacter sakazakii infections associated with the use of powdered infant formula – Tennessee, 2001. *Morbidity and Mortality Weekly Report*, 2002, 51:297–300.

107. Van Acker J, DeSmet F, Muyldermans G. Outbreak of necrotising enterocolitis associated with Enterobacter sakazakii in powdered milk formula. *Journal of Clinical Microbiology*, 2001, 39:293–7.

108. Simmons BP, Gelfand MS, Haas M. Enterobacter sakazakii infections in neonates associated with intrinsic contamination of a powdered formula. *Infection Control and Hospital Epidemiology*, 1989, 10:398–401.

109. World Health Organization. Enterobacter sakazakii *and other microorganisms in powdered infant formula: meeting report*. MRA Series 6, Geneva, World Health Organization, 2004 (http://www.who.int/foodsafety/publications/micro/en/es.pdf).

110. Volpe JJ. *Neurology of the newborn*. 3rd ed. Philadelphia, WB Saunders, 1995.

111. Stevenson RD, Allaire JH. The development of normal feeding and swallowing. *Pediatric Clinics of North America*, 1991, 38:1439–53.

112. McMillen IC, Kok JS, Adamson TM. Development of circadian sleep-wake rhythms in preterm and full term infants. *Pediatric Research*, 1991, 29:381–4.

113. Shimada M, Segawa M, Higurashi M. Development of the sleep and wakefulness rhythm in preterm infants discharged from a neonatal care unit. *Pediatric Research* 1993, 33:159–63.

114. Saint-Anne Dargassies S. *Neurological development in the full term and premature neonate*. New York, Excerpta Medica, 1977.

115. Parmelee AH, Wenner WH, Akiyama Y. Sleep states in premature infants. *Developmental Medicine and Child Neurology*, 1967, 9:70–7.

116. Lang S. Breastfeeding special care babies, 2nd ed. Edinburgh, Bailliere Tindall, 2002.

117. Nyqvist KH, Sjoden P-O, Ewald U. The development of preterms infants' breastfeeding behaviour. *Early Human Development*,1999, 55:247–264.

118. Bu'Lock F, Woolridge MW, Baum JD. Development of coordination of sucking, swallowing and breathing: ultrasound study of term and preterm infants. *Developmental Medicine and Child Neurology*,1990, 32:669–78.

119. Weber F, Woolridge MW, Baum JD. An ultrasonographic study of the organisation of sucking and swallowing by newborn infants. *Developmental Medicine and Child Neurology*, 1986, 28:19–24.

120. Bosma JF, Hepburn LG, Josell SD. Ultrasound demonstration of tongue motions during suckle feeding. *Developmental Medicine and Child Neurology*, 1990, 32:223–9.

121. Naylor AJ, Morrow AL, eds. *Developmental readiness of normal full term infants to progress from exclusive breastfeeding to the introduction of complementary foods: reviews of the relevant literature concerning infant immunologic, gastrointestinal, oral motor and maternal reproductive and lactational development*, Washington, D.C., Wellstart International and the LINKAGES Project/Academy for Educational Development, 2001.

122. Kalhan SC et al. Role of glucose in the regulation of endogenous glucose production in the human newborn. *Pediatric Research*, 1996, 20:49–52.

123. Gerich JE. Control of glycaemia. *Baillieres Clinical Endocrinology and Metabolism*, 1993, 7:551–586.

124. Lucas A, Bloom SR, Green AA. Gastrointestinal peptides and the adaptation to extrauterine nutrition. *Canadian Journal of Physiology and Pharmacology*, 1985, 1985:527–37.

125. Lucas A, Bloom SR, Aynsley-Green A. Gut hormones and minimal enteral feeding. *Acta Pediatrica Scandinavica*, 1986, 75:719–23.

126. Lucas A, Boyes S, Bloom SR, Aynsley-Green A. Metabolic and endocrine responses to a milk feed in six-day-old term infants: differences between breast and cow's milk formula feeding. *Acta Pediatrica Scandinavica*, 1981, 70:195–200.

127. Mayne A, Hughes CA, Sule D, Brown GA, McNeish AS. Development of intestinal disaccaridases in preterm infants. *Lancet* 1983;II:622–3.

128. Dweck HS, Cassady G. Glucose intolerance in infants of very low birth weight. I. Incidence of hyperglycemia in infants of birth weights 1,100 grams or less. *Pediatrics*, 1974 , 53(2):189–95.

129. Mena P, Llanos A, Uauy R. Insulin homeostasis in the extremely low birth weight infant. *Seminars in Perinatology*, 2001, 25(6):436–46.

130. Lebenthal E, Leung YK: Alternative pathways of digestion and absorption in the newborn. In: Lebenthal E, ed. *Gastroenterology and Nutrition in Infancy*, New York, Raven Press Ltd, 1989: 3–7.

131. Ameen YZ, Powell SK. Quantitative fecal carbohydrate excretion in premature infants. *American Journal of Clinical Nutrition*, 1989, 49:1238–1242.

132. Kien CL et al. Stable isotope model for estimating colonic acetate production in premature infants. *Gastroenterology*, 1992, 102:1458–1466.

133. Lebenthal E, Leung Y. Feeding the premature and comprismied infant. Gastrointestinal considerations. *Pediatric Clinics of North America*, 1988, 35:215–8.

134. Bissett WM et al. Postprandial motor response of the small intestine to enteral feeds in preterm infants. *Archives of Disease in Childhood*, 1989, 64:1356–61.

135. Bisset WM et al. Ontogeny of fasting small intestinal motor activity in the human infant. *Gut*, 1988, 29(4):483–8.

136. Berseth CL. Neonatal small intestinal motility: motor responses to feeding in term and preterm infants. *Journal of Pediatrics*, 1990, 117(5):777–82.

137. Berseth CL et al. Responses of gastrointestinal peptides and motor activity to milk and water feedings in preterm and term infants. *Pediatric Research*, 1992, 31(6):587–90.

138. Berseth CL. Gut motility and the pathogenesis of necrotizing enterocolitis. *Clinics in Perinatology*, 1994, 21(2):263–70.

139. Baker JH, Berseth CL. Duodenal motor responses in preterm infants fed formula with varying concentrations and rates of infusion. *Pediatric Research*, 1997, 42(5):618–22.

140. Yu VYH, Rolfe P. Effect of feeding on ventilation and respiratory mechanics in newborn infants. *Archives of Disease in Childhood*, 1976, 51:310–313.

141. Heird WC, Schwartz SM, Hansen IH. Colostrum induced enteric mucosal growth in beagle puppies. *Pediatric Research*, 1984, 18:512–5.

142. American Academy of Pediatrics Work Group on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics*, 1997, 100:1035–1039.

143. WHO/UNICEF Joint Statement. *Protection, Promotion and Support of Breastfeeding: the Ten Steps to Successful Breastfeeding*, Geneva and New York, World Health Organization and United Nations Children's Fund, 1999.

144. World Health Organization. *Protecting, promoting and supporting breastfeeding: the special role of maternity services*. Geneva, World Health Organization, 1989.

145. Kramer MS, Kakuma R. *The optimal duration of exclusive breastfeeding: a systematic review*. (WHO/NHD/01.08.WHO/FCH/CAH/01.23). Geneva, World Health Organization, 2002.

146. Narayanan I et al. Partial supplementation with expressed breast milk for prevention of infection in the low birth weight infant. *Lancet*, 1980, 2:561–563.

147. Narayanan I et al. Administration of colostrum for the prevention of infection in the low birth weight infant in a developing country. *Journal of Tropical Pediatrics*, 1983, 29(4):197–200.

148. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. *Lancet*, 1990, 336:1519–1523.

149. Hylander MA, Strobino DM, Dhanireddy R. Human milk feedings and infection among very low birth weight infants. *Pediatrics*, 1998, 102: 1–6

150. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics*, 1999, 103:1150–1157

151. Doyle LW et al. Breastfeeding and intelligence. *Lancet*, 1992, 339:744–5.

152. Lucas A et al. Breast milk and subsequent intelligence quotient in children born preterm. *Lancet*, 1992, 339:261–264.

153. Pollock JI. Mother's choice to provide breast milk and developmental outcome. *Archives of Disease in Childhood*, 1989, 64(5)763–4.

154. Rao MR et al. Effect of breastfeeding on cognitive development of infants born small for gestational age. *Acta Paediatrica*, 2002, 91:267–74.

155. Morley R et al. Mothers' choice to provide breast milk and developmental outcome. *Archives of Disease in Childhood*,1988, 63:1382–1385.

156. Anderson JW et al. Breastfeeding and cognitive development: a meta-analysis. *American Journal of Clinical Nutrition*, 1999, 70:525–35.

157. O'Connor DL et al. Growth and development of premature infants fed predominantly human milk, predominantly premature infant formula, or a combination of human milk and premature formula. *Journal of Pediatric Gastroenterology and Nutrition*, 2003, 37(4):437–46.

158. Ounsted M, Moar VA, Scott A. Neurological development of small-for-gestational age babies during the first year of life. *Early Human Development*, 1988, 16(2–3):163–72.

159. Morley R et al. Neurodevelopment in children born small for gestational age: a randomized trial of nutrient-enriched versus standard formula and comparison with a reference breastfed group. *Pediatrics*, 2004, 113(3 Pt 1):515–21.

160. Lucas A et al. Randomized trial of nutrient-enriched formula versus standard formula for postdischarge preterm infants. *Pediatrics*, 2001, 108:703–11.

161. Fewtrell MS et al. Catch-up growth in small-for-gestational-age term infants: a randomized trial. *American Journal of Clinical Nutrition*, 2001, 516–23.

162. Iwai Y et al. Iron status in low birth weight infants on breast and formula feeding. European *Journal of Pediatrics*, 1986, 145:63–65.

163. James JA, Combes M. Iron deficiency in the premature infant: significance and prevention by the intramuscular administration of iron dextran. *Pediatrics*, 1960, 26:368–374.

164. Widdershoven J et al. Plasma concentrations of vitamin K1 and PIVKA-II in bottle-fed and breast-fed infants with and without vitamin K prophylaxis at birth. European *Journal of Pediatrics*, 1988, 148:139–142.

165. Atkinson SA, Radde IC, Anderson GH. Macromineral balances in premature infants fed their own mothers' milk or formula. *Journal of Pediatrics*, 1983, 102:99–106.

166. Rowe JC et al. Nutritional hypophosphatemic rickets in a premature infant fed breast milk. *New England Journal of Medicine*, 1979, 300:293–296.

167. Pettifor JM et al. Mineral homeostasis in very low birth weight infants fed either own mother's milk or pooled pasteuised preterm milk. *Journal of Pediatric Gastroenterology and Nutrition*, 1986, 5:248–53.

168. Pettifor JM et al. Bone mineralization and mineral homeostasis in very low-birth-weight infants fed either human milk or fortified human milk. *Journal of Pediatric Gastroenterology and Nutrition*, 1989, 8:217–224.

169. Friel J et al. A comparison of the zinc, copper, and manganese status of very low weight preterm and full-term infants during the first twelve months. *Acta Pediatrica Scandinavica*, 1984, 73:596–601.

170. Friel JK et al. Dietary zinc intake and growth during infancy. *Journal of Pediatric Gastroenterology and Nutrition*, 1985, 4(5):746–751.

171. Woodruff CW et al. Vitamin A status of preterm infants: the influence of feeding and vitamin supplements. *American Journal of Clinical Nutrition*, 1986, 44:384–389.

172. Peeples JM et al. Vitamin A status of preterm infants during infancy. *American Journal of Clinical Nutrition*, 1991, 53:1455–1459.

173. Robertson I. Follow-up study of clinical rickets in Cape Town infants. *South African Medical Journal*, 1970, 44(12):368.

174. McGuire W, Anthony MY. Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review. *Archives of Disease in Childhood Fetal and Neonatal Edition*, 2003, 88:F11–14.

175. Svenningsen NW, Lindroth M, Linquist B. A comparative study of varying protein intake in low birth weight infant feeding. *Acta Pediatrica Scandinavica* Supplement, 1982, 296:28–31.

176. Gross SJ. Growth and biochemical response of preterm infants fed human milk or modified infant formula. *New England Journal of Medicine*, 1983, 308:237–241.

177. Tyson JE et al. Growth, metabolic response, and development in very-low-birth-weight infants fed banked human milk or enriched formula. I. Neonatal findings. *Journal of Pediatrics*, 1983, 103:95–104.

178. Schanler RJ et al. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. *Pediatrics*, 2005, 116(2):400–6.

179. Davies DP. Adequacy of expressed breast milk for early growth of preterm infants. *Archives of Disease in Childhood*, 1977, 52:296–301.

180. Raiha NC et al. Milk protein quantity and quality in low-birthweight infants: I. Metabolic responses and effects on growth. *Pediatrics*, 1976, 57:659–684.

181. Schultz K, Soltesz G, Mestyan J. The metabolic consequences of human milk and formula feeding in premature infants. *Acta Paediatrica Scandinavica*, 1980, 69:647–652.

182. Morley R, Lucas A. Randomized diet in the neonatal period and growth performance until 7.5–8 y of age in preterm children. *American Journal of Clinical Nutrition*, 2000, 71:822–828.

183. Singhal A et al. Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomized study. *Lancet*, 2004, 363:1571–8.

184. Lucas A, Morley R. Does early nutrition in infants born before term programme later blood pressure. *British Medical Journal*, 1994, 30: 304–8.

185. Lucas A et al. Multicentre trial on feeding low birthweight infants: effects of diet on early growth. *Archives of Disease in Childhood*, 1984, 59:722–730.

186. Fewtrell MS et al. Bone mineralisation and turnover in preterm infants at 8–12 years of age: the effect of early diet. *Journal of Bone and Mineral Research*, 1999, 14:810–820.

187. Bhandari N et al. Effect of community-based promotion of exclusive breastfeeding on diarrhoeal illness and growth: a cluster randomized controlled trial. *Lancet*, 2003, 26;361:1418–23.

188. Dewey KG et al. Effects of exclusive breastfeeding for four versus six months on maternal nutritional status and infant motor development: results of two randomized trials in Honduras. *Journal of Nutrition*, 2001, 131:262–7.

189. Dewey KG et al. Age of introduction of complimentary foods and growth of full term, low birth weight, breastfed infants: a randomized intervention study in Honduras. *American Journal of Clinical Nutrition*, 1999, 69:679–86.

190. Marriott LD et al. Weaning preterm infants: a randomized controlled trial. *Archives of Disease in Childhood Fetal and Neonatal Edition*, 2003, 88:F302–F307.

191. Dewey KG, Cohen RJ, Brown KH. Exclusive breast-feeding for 6 months, with iron supplementation, maintains adequate micronutrient status among term, low-birthweight, breast-fed infants in Honduras. *Journal of Nutrition*, 2004, 134:1091–8.

192. Coutsoudis A et al. Effect of vitamin A supplementation on morbidity of low-birth-weight neonates. *South African Medical Journal*, 2000, 90:730–6.

193. Humphrey JH et al. Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *Journal of Pediatrics*, 1996; 128:489–96.

194. Rahmathullah L et al. Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomized trial in southern India. *British Medical Journal*, 2003, 327:254–257.

195. Malaba LC et al. Effect of postpartum maternal or neonatal vitamin A supplementation on infant mortality among infants born to HIV-negative mothers in Zimbabwe. *American Journal of Clinical Nutrition*, 2005, 81(2):454–60.

196. Lucas A et al. High alkaline phosphatase activity and growth in preterm neonates. *Archives of Disease in Childhood*, 1989, 64:902–909.

197. Evans JR et al. Effect of high-dose vitamin D supplementation on radiographically detectable bone disease of very low birth weight infants. *Journal of Pediatrics*, 1989, 115:779–786.

198. Backstrom MC et al. Randomised controlled trial of vitamin D supplementation on bone density and biochemical indices in preterm infants. *Archives of Disease in Childhood Fetal and Neonatal Edition*, 1999, 80:161–6.

199. Backstrom MC et al. The long term effect of early mineral, vitamin D and breastmilk intake on bone mineral status in 9 to 11 year old children born prematurely. *Journal of Pediatric Gastroenterology and Nutrition*, 1999, 29:575–82.

200. Puckett RM, Offringa M. Prophylactic vitamin K for vitamin K deficiency bleeding in neonates. *Cochrane Database of Systematic Reviews* 2000, Issue 4. Art. No.: CD002776. DOI: 10.1002/14651858.CD002776.

201. Golding J, Paterson M, Kinlen LJ. Factors associated with childhood cancer in a national cohort study. *British Journal of Cancer*, 1990, 62:304–8.

202. Golding J et al. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *British Medical Journal*, 1992, 305:341–6.

203. Roman E et al. Vitamin K and childhood cancer: analysis of individual patient data from six case-control studies. *British Journal of Cancer*, 2002, 86(1):63–9.

204. Sann L et al. Serum vitamin K1 concentrations after oral administration of vitamin K1 in low birth weight infants. *Journal of Pediatrics*, 1985, 107:608–611.

205. Kumar D et al. Vitamin K status of premature infants: implications for current recommendations. *Pediatrics*, 2001, 108:1117–22.

206. Costakos DT et al. Vitamin K prophylaxis for premature infants: 1 mg versus 0.5 mg. American *Journal of Perinatology*, 2003, 20(8):485–90.

207. Doyle JJ, Zipursky A. Neonatal blood disorders. In: Sinclair JC, Bracken MB, eds., *Effective care of the newborn infant*, Oxford, Oxford University Press, 1992:94–140.

208. Lundstrom U, Siimes AM, Dallman PR. At what age does iron supplementation become necessary in low birth weight infants? *Journal of Pediatrics*, 1977, 91:878–883.

209. Gorten MK, Cross ER. Iron absorption in premature infants II. Prevention of iron deficiency. *Journal of Pediatrics*, 1964, 64:509–20.

210. Hammond D, Murphy A. The influence of exogenous iron on formation of haemoglobin in the premature infant. *Pediatrics*, 1960, 25:362–74.

211. Aggarwal D et al. Haematological effect of iron supplementation in breast fed term low birth weight infants. *Archives of Disease in Childhood*, 2005, 90(1):26–9.

212. Franz AR et al. Prospective randomized trial of early versus late enteral iron supplementation in infants with a birth weight of less than 1301 grams. *Pediatrics*, 2000, 106:700–706.

213. Siimes MA. Iron requirements in low birthweight infants. *Acta Paediatrica Scandinavica* supplement, 1982, 296:101–103

214. Lackmann GM, Hesse L, Tollner U. Reduced iron-associated antioxidants in premature newborns suffering intracerebral hemorrhage. *Free Radical Biology and Medicine*, 1996, 20:407–409.

215. Scott PH et al. Effect of gestational age and intrauterine nutrition on plasma transferrin and iron in the newborn. *Archives of Disease in Childhood*, 1975, 50:796–798.

216. Sazawal S et al. Zinc supplementation in infants born small for gestational age reduces mortality: A prospective, randomized, controlled trial. *Pediatrics*, 2001, 108:1280–6.

217. Lira PI, Ashworth A, Morris SS. Effect of zinc supplementation on the morbidity, immune function and growth of low birth weight, full term infants in northeast Brazil. *American Journal of Clinical Nutrition*, 1998, 68:418S–24S.

218. Sur D et al. Impact of zinc supplementation on diarrheal morbidity and growth pattern of low birth weight infants in Kolkata, India: a randomized, double-blind, placebo-controlled, community-based study. *Pediatrics*, 2003, 112(6 Pt 1):1327–32.

219. Black MM et al. Cognitive and motor development among small-for-gestational-age infants: impact of zinc supplementation, birth weight, and caregiving practices. *Pediatrics*, 2004, 113(5):1297–305.

220. Ashworth A et al. Zinc supplementation, mental development and behaviour in low birth weight infants in north east Brazil. *European Journal of Clinical Nutrition*, 1998, 52:223–7.

221. Castillo-Duran C et al. Zinc supplementation and growth of infants born small for gestational age. *Journal of Pediatrics*, 1995, 127:206–11.

222. Wauben I, Gibson R, Atkinson S. Premature infants fed mothers milk to 6 months corrected age demonstrated adequate growth and zinc status in the first year. *Early Human Development*, 1999, 54:181–94.

223. Schanler RJ, Abrams SA, Garza C. Mineral balance studies in very low birth weight infants fed human milk. *Journal of Pediatrics*, 1988, 113: 230–7.

224. Horsman A, Ryan SW, Truscott JG. Bone mineral content and 'body size 65 to 100 weeks' postconception in preterm and full term infants. *Archives of Disease in Childhood*, 1985, 64:1579–86.

225. Brooke LA. Metabolic bone disease in preterm infants. *Archives of Disease in Childhood*, 1985; 60:682–5.

226. Schanler RJ et al. Bone mineralization outcomes in human milk-fed preterm infants. *Pediatric Research*, 1992, 31(6):583–6.

227. Takada M et al. Trace elements and mineral requirements for very low birth weight infants in rickets of prematurity. *Early Human Development*, 1992, 29:333–8.

228. Schanler RJ, Abrams SA. Postnatal attainment of intrauterine macromineral accretion rates in low birth weight infants fed fortified human milk. *Journal of Pediatrics*, 1995, 26:441–7.

229. Bishop NJ, King FJ, Lucas A. Increased bone mineral content of preterm infants fed with a nutrient enriched formula after discharge from hospital. *Archives of Disease in Childhood*, 1993, 68:573–8.

230. Chan GM. Growth and bone mineral status of discharged very low birth weight infants fed different formulas or human milk. *Journal of Pediatrics*, 1993, 193:439–43.

231. Laing IA et al. Rickets of prematurity: calcium and phosphorus supplementation. *Journal of Pediatrics*, 1985, 106(2):265–8.

232. Holland PC et al. Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight infants. *Lancet*, 1990, 335(8691):697–701.

233. Kuschel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD000343. DOI: 10.1002/14651858.CD000343.pub2.

234. Kashyap S et al. Growth, nutrient retention, and metabolic response of low-birth-weight infants fed supplemented and unsupplemented preterm human milk. *American Journal of Clinical Nutrition*, 1990, 52:254–262.

235. Zuckerman M, Pettifor JM. Rickets in very-low-birth-weight infants born at Baragwanath Hospital. *South African Medical Journal*, 1994, 84:216–20.

236. Faerk J et al. Diet, growth, and bone mineralization in premature infants. *Advances in Experimental Medicine and Biology*, 2001, 501:479–83.

237. Carey DE et al. Growth and phosphorus metabolism in premature infants fed human milk, fortified human milk, or special premature formula. Use of serum procollagen as a marker of growth. *American Journal of Diseases of Children*, 1987, 141:511–515.

238. Greer FR, McCormick A. Improved bone mineralization and growth in premature infants fed fortified own mother's milk. *Journal of Pediatrics*, 1988, 112:961–969.

239. Nicholl RM, Gamsu HR. Changes in growth and metabolism in very low birthweight infants fed with fortified breast milk. *Acta Paediatrica*, 1999, 88:1056–61.

240. Polberger SKT, Axelsson IA, Räihä NCE. Growth of very low birth weight infants on varying amounts of human milk protein. *Pediatric Research*, 1989, 25:414–419.

241. Wauben IP et al. Moderate nutrient supplementation of mother's milk for preterm infants supports adequate bone mass and short-term growth: a randomized, controlled trial. *American Journal of Clinical Nutrition*, 1998, 67:465–472.

242. Gross SJ. Bone mineralization in preterm infants fed human milk with and without mineral supplementation. *Journal of Pediatrics*, 1987;111:450–458.

243. Modanlou HD et al. Growth, biochemical status, and mineral metabolism in very-low-birth-weight infants receiving fortified preterm human milk. *Journal of Pediatric Gastroenterology and Nutrition*, 1986, 5:762–767.

244. Lucas A et al. Early diet in preterm babies and developmental status at 18 months. *Lancet*, 1990, 335:1477–1481.

245. Lucas A, Morely R, Cole TJ. Randomized trial of early diet in preterm babies and later intelligence quotient. *British Medical Journal*, 1998, 317:1481–7.

246. Cooke RJ et al. Feeding preterm infants after hospital discharge: growth and development at 18 months of age. *Pediatric Research*, 2001, 49:719–22.

247. Henderson G, Fahey T, McGuire W. Calorie and protein-enriched formula versus standard term formula for improving growth and development in preterm or low birth weight infants following hospital discharge. *Cochrane Database of Systematic Reviews*, 2005, Issue 2. Art. No.: CD004696. DOI: 10.1002/14651858.CD004696.pub2.

248. Carver JD et al. Growth of preterm infants fed nutrient-enriched or term formula after hospital discharge. *Pediatrics*, 2001, 107:683–689.

249. Litmanovitz I et al. Bone strength and growth of preterm infants fed nutrient-enriched or term formula after hospital discharge. *Pediatric Research*, 2004, 274A.

250. de Curtis M, Pieltain C, Rigo J. Body composition in preterm infants fed standard term or enriched formula after hospital discharge. European *Journal of Nutrition*, 2002, 41:177–82.

251. Malhotra N et al. A controlled trial of alternative methods of oral feeding in neonates. *Early Human Development*, 1999, 54:29–38.

252. Collins CT et al. Effect of bottles, cups, and dummies on breast feeding in preterm infants: a randomised controlled trial. *British Medical Journal*, 2004, 329(7459):193–8.

253. Rocha N, Martinez F, Jorge S. Cup or bottle for preterm infants: effects on oxygen saturation, weight gain and breastfeeding. *Journal of Human Lactation*, 2002, 18:132–137.

254. Lang S, Lawrence CJ, Orme RL. Cup feeding: an alternative method of infant feeding. *Archives of Disease in Childhood*, 1994, 71:365–9.

255. Mosley C, Whittle C, Hicks C. A pilot study to assess the viability of a randomized controlled trial of methods of supplementary feeding of breast-fed pre-term babies. *Midwifery*, 2001, 17(2):150–7.

256. Howard CR et al. Physiological stability of newborns during cup- and bottle-feeding. *Pediatrics*, 1999, 104:1204–6.

257. Marinelli KA, Burke GS, Dodd VL. A comparison of the safety of cupfeedings and bottlefeedings in premature infants whose mothers intend to breastfeed. *Journal of Perinatology*, 2001, 21:355.

258. Dsilna A et al. Continuous feeding promotes gastrointestinal tolerance and growth in very low birth weight infants. *Journal of Pediatrics*, 2005, 147(1):43–9.

259. Stocks J. Effect of nasogastric tubes on nasal resistance during infancy. *Archives of Disease in Childhood*, 1980, 55:17–21.

260. Greenspan JS et al. Neonatal gastric intubation: differential respiratory effects between nasogastric and orogastric tubes. *Pediatric Pulmonology*, 1990, 8(4):254–8.

261. Daga SR, Lunkad NG, Daga AS, Ahuja VK. Orogastric versus nasogastric feeding of newborn babies. *Tropical Doctor*, 1999, 29(4):242–3.

262. Premji S, Chessell L. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. *Cochrane Database of Systematic Reviews*, 2002, Issue 4. Art. No.: CD001819. DOI: 10.1002/14651858.CD001819.

263. Akintorin SM et al. A prospective randomized trial of feeding methods in very low birth weight infants. *Pediatrics*, 1997, 100:E4.

264. Schanler RJ et al. Feeding strategies for premature infants: Randomized trial of gastrointestinal priming and tube-feeding method. *Pediatrics*, 1999, 103:434–39.

265. Silvestre MA et al. A prospective randomized trial comparing continuous versus intermittent feeding method in very low birth weight neonates. *Journal of Pediatrics*, 1996, 128:748–52.

266. Toce SS, Keenan WJ, Homan SM. Enteral feeding in very-low-birth-weight infants. A comparison of two nasogastric methods. *American Journal of Diseases of Children*, 1987, 141:439–44.

267. Narayanan I, Singh B, Harvey D. Fat loss during feeding of human milk. *Archives of Disease in Childhood*, 1984, 59(5):475–7.

268. Stocks RJ et al. Loss of breast milk nutrients during tube feeding. *Archives of Disease in Childhood*, 1985, 60(2):164–6.

269. Brooke OG, Barley J. Loss of energy during continuous infusions of breast milk. *Archives of Disease in Childhood*, 1978, 53(4):344–5.

270. Bauer K et al. Body composition, nutrition, and fluid balance during the first two weeks of life in preterm neonates weighing less than 1500 grams. *Journal of Pediatrics*, 1991,118:615–620.

271. Tyson JE, Kennedy KA. Trophic feedings for parenterally fed infants. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD000504. DOI: 10.1002/14651858.CD000504.pub2.

272. Cornblath M et al. A controlled study of early fluid administration on survival of low birth weight infants. *Pediatrics*, 1966, 4:547–54.

273. Wharton BA, Bower BD. Immediate or later feeding for premature babies? A controlled trial. *Lancet*, 1965, 2:969–72.

274. Smallpeice V, Davies PA. Immediate feeding of premature infants with undiluted breastmilk. *Lancet*, 1964, 2:1349–52.

275. Kennedy KA, Tyson JE. Rapid versus slow rate of advancement of feedings for promoting growth and preventing necrotizing enterocolitis in parenterally fed low-birth-weight infants. *Cochrane Database of Systematic Reviews*, 1998, Issue 4. Art. No.: CD001241. DOI: 10.1002/14651858.CD001241.

276. Book LS, Herbst JJ, Jung AL. Comparison of fast- and slow-feeding rate schedules to the development of necrotizing enterocolitis. *Journal of Pediatrics*, 1976, 89:463–466.

277. Caple JI et al. The effect of feeding volume on the clinical outcome in premature infants. *Pediatric Research*, 1997, 41:1359A.

278. Rayyis SF et al. Randomized trial of "slow" versus "fast" feed advancements on the incidence of necrotizing enterocolitis in very low birth weight infants. *Journal of Pediatrics*, 1999, 134:293–7.

279. Caple J et al. Randomized, controlled trial of slow versus rapid feeding volume advancement in preterm infants. *Pediatrics*, 2004, 114(6):1597–600.

280. Berseth CL, Bisquera JA, Paje VU. Prolonging small feeding volumes early in life decreases the incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*, 2003, 111(3):529–34.

281. Kuschel CA et al. A randomized trial of enteral feeding volumes in infants born before 30 weeks' gestation. *Journal of Paediatrics and Child Health*, 2000; 36:581–6.

282. Pauls J, Bauer K, Versmold H. Postnatal body weight curves for infants below 1000 g birth weight receiving early enteral and parenteral nutrition. European *Journal of Pediatrics*, 1998, 157:416–421.

283. Hardy J, Goldstein E. The feeding of premature infants. *Journal of Pediatrics*, 1951, 38:154–157.

284. Horton F, Lubchenco L, Gordon H. Self-regulatory feeding in a premature nursery. *The Yale Journal of Biology and Medicine*, 1952, 24:263–272.

285. Collinge JM et al. Demand versus scheduled feedings for premature infants. *Journal of Obstetric, Gynecologic and Neonatal Nursing*, 1982, 11:362–367.

286. Anderson GC. Self-regulatory gavage to bottle feeding for preterm infants: effect on behavioral state, energy expenditure, and weight gain. In: Funk SG et al, eds. *Key Aspects of Recovery*. New York, Springer Publishing Company; 1990:83–129.

287. Saunders RB, Friedman CB, Stramoski PR. Feeding pre-term infants: schedule or demand? *Journal of Obstetric, Gynecologic and Neonatal Nursing*, 1991; 20:212–218.

288. Pridham K et al. The effects of prescribed versus ad libitum feedings and formula caloric density on premature infant dietary intake and weight gain. *Nursing Research*, 1999, 48:86–93.

289. McCain GC et al. A feeding protocol for healthy preterm infants that shortens time to oral feeding. *Journal of Pediatrics*, 2001, 139:374–379.

290. Crosson DD, Pickler RH. An integrated review of the literature on demand feedings for preterm infants. *Advances in Neonatal Care*, 2004, 4(4):216–25.

291. Cattaneo A et al. Kangaroo mother care for low birthweight infants: a randomized controlled trial in different settings. *Acta Paediatrica*, 1998, 87:976–85.

292. Charpak N et al. Kangaroo mother versus traditional care for newborn infants <2000 grams: a randomized controlled trial. *Pediatrics*, 1997, 100:682–8.

293. Charpak N et al. A randomized, controlled trial of Kangaroo Mother Care: Results of follow-up at 1 year of corrected age. *Pediatrics*, 2001, 108:1072–9

294. Worku B, Kassie A. Kangaroo mother care: a randomized controlled trial on effectiveness of early kangaroo mother care for the low birthweight infants in Addis Ababa, Ethiopia. *Journal of Tropical Pediatrics*, 2005, 51(2):93–7.

295. Bergman NJ, Jurisoo LA. The 'kangaroo-method' for treating low birth weight babies in a developing country. *Tropical Doctor*, 1994, 24(2):57–60.

296. Lincetto O, Nazir AI, Cattaneo A. Kangaroo mother care with limited resources. *Journal of Tropical Pediatrics*, 2000, 46(5):293–5.

297. Sloan NL et al. Kangaroo mother method: randomized controlled trial of an alternative method of care for stabilised low-birthweight infants. *Lancet*, 1994, 344:782–5.

298. Conde-Agudelo A, Diaz-Rossello JL, Belizan JM. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database of Systematic Reviews*, 2003, Issue 2. Art. No.: CD002771. DOI: 10.1002/14651858.CD002771.

299. Anderson GC et al. Early skin-to-skin contact for mothers and their healthy newborn infants. *Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD003519. DOI: 10.1002/14651858.CD003519.

300. Ferber SG, Makhoul IR. The effect of skin-to-skin contact (kangaroo care) shortly after birth on the neurobehavioral responses of the term newborn: a randomized, controlled trial. *Pediatrics*, 2004, 113(4):858–65.

301. Whitelaw A et al. Skin to skin contact for very low birthweight infants and their mothers. *Archives of Disease in Childhood*, 1988, 63(11):1377–81.

302. Hurst NM et al. Skin-to-skin holding in the neonatal intensive care unit influences maternal milk volume. *Journal of Perinatology*, 1997, 17(3):213–7.

303. Bergman NJ, Linley LL, Fawcus SR. Randomized controlled trial of skin-to-skin contact from birth versus conventional incubator for physiological stabilization in 1200– to 2199–gram newborns. *Acta Paediatrica*, 2004, 93(6):779–85.

304. Quasem I et al. Adaptation of kangaroo mother care for community-based application. *Journal of Perinatology*, 2003, 23(8):646–51.

305. World Health Organization. *Kangaroo Mother Care: a Practical Guide*. Geneva, World Health Organization, 2003 (ISBN-13: 9789241590358, ISBN-10: 9241590351).

306. Pinelli J, Symington A. Non-nutritive sucking for promoting physiologic stability and nutrition in preterm infants. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD001071. DOI: 10.1002/14651858.CD001071.pub2.

307. Field T et al. Non-nutritive sucking during tube feedings: Effects on preterm neonates in an intensive care unit. *Pediatrics*, 1982, 70:381–384.

308. Mattes RD et al. Effects of sweet taste stimulation on growth and sucking in preterm infants. *Journal of Obstetric, Gynecologic and Neonatal Nursing*, 1996, 25:407–414.

309. Ernst JA et al. Lack of improved growth outcome related to non-nutritive sucking in very low birth weight premature infants fed a controlled nutrient intake: A randomized prospective study. *Pediatrics*, 1989, 83:706–716.

310. Bernbaum JC et al. Nonnutritive sucking during gavage feeding enhances growth and maturation in premature infants. *Pediatrics*, 1983, 71:41–45.

311. Karan S, Rao SS. Benefits of early maternal participation in care of low birth weight infants leading to early discharge. *Journal of Tropical Pediatrics*, 1983, 29(2):115–8.

312. Narayanan I et al. Maternal participation in the care of the high risk infant: follow-up evaluation. *Indian Pediatrics*, 1991, 28(2):161–7.

313. Bhutta ZA et al. Reducing length of stay in hospital for very low birthweight infants by involving mothers in a stepdown unit: an experience from Karachi (Pakistan). *British Medical Journal*, 2004, 329(7475):1151–5.

314. Bhargava SK et al. Early discharge of infants with birth weight of 1800 g or less. *Indian Pediatrics*, 1980, 17(5):425–9.

315. Dillard RG, Korones SB. Lower discharge weight and shortened nursery stay for low-birth-weight infants. *New England Journal of Medicine*, 1973, 288(3):131–3.

316. Lefebvre F, Veilleux A, Bard H. Early discharge of low birthweight infants. *Archives of Disease in Childhood*, 1982, 57(7):511–3

317. Brooten D et al. A randomized clinical trial of early hospital discharge and home follow-up of very-low-birth-weight infants. *New England Journal of Medicine*, 1986, 315(15):934–9.

318. Casiro OG et al. Earlier discharge with community-based intervention for low birth weight infants: a randomized trial. *Pediatrics*, 1993, 92(1):128–34.

319. Gunn TR et al. Does early hospital discharge with home support of families with preterm infants affect breastfeeding success? A randomized trial. *Acta Paediatrica*, 2000, 89(11):1358–63.

320. Cruz H et al. Early hospital discharge of preterm very low birth weight infants. *Journal of Perinatology*, 1997, 17(1):29–32.

321. Davies DP, Derbyshire F. Early discharge of low birthweight infants. *Archives of Disease in Childhood*, 1983, 58(1):79.

322. Collins CT, Makrides M, McPhee AJ. Early discharge with home support of gavage feeding for stable preterm infants who have not established full oral feeds. *Cochrane Database of Systematic Reviews*, 2003, Issue 4. Art. No.: CD003743. DOI: 10.1002/14651858.CD003743.

323. Örtenstrand A, Waldenström U, Winbladh B. Early discharge of preterm infants needing limited special care, followed by domiciliary nursing care. *Acta Paediatrica* 1999;88:1024–30.

324. Sikorski J et al. Support for breastfeeding mothers: a systematic review. *Paediatric and Perinatal Epidemiology*, 2003, 17(4):407–17.

325. Agrasada GV et al. Postnatal peer counselling on exclusive breastfeeding of low-birthweight infants: a randomized, controlled trial. *Acta Paediatrica*, 2005, 94(8):1109–15.

326. Pinelli J, Atkinson S, Saigal S. Randomized trial of breastfeeding support in very low birth weight infants. *Archives of Pediatric and Adolescent Medicine*, 2001, 155:548–53.

327. Haider R et al. Effect of community-based peer counsellors on exclusive breastfeeding practices in Dhaka, Bangladesh: a randomized controlled trial. *Lancet*, 2000, 356(9242):1643–7.

328. Ashworth A et al. Impact of a breastfeeding peer counselling intervention on growth of infants. *Annals of Nutrition and Metabolism*, 2001, 45 (Supplement 1): 435.

329. Morrow A et al. Efficacy of home-based peer counselling to promote exclusive breastfeeding: a randomized controlled trial. *Lancet*, 1999, 353(9160);1226–31.

330. Ehrenkranz RA et al. Breastfeeding and premature infants. Incidence and success. *Pediatric Research*, 1985, 19:199.

331. Pereira GR et al. Breastfeeding in neonatal intensive care. *Perinatology and Neonatology*, 1984, 8:35–42.

332. Bell EH, Geyer J, Jones L. A structured intervention improves breastfeeding success for ill or preterm infants. *American Journal of Maternal and Child Nursing*, 1995, 20:309–14.

333. Ehrenkranz RA, Ackerman BA. Metoclopramide effect on faltering milk production by mothers of premature infants. *Pediatrics*, 1986, 78(4):614–20

334. de Silva OP. Effect of Domperidone on milk production in mothers of premature newborns: a randomized double blind placebo controlled trial. *Canadian Medical Association Journal*, 2001, 164:17–21.

335. Hansen WF et al. Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. *Obstetrics and Gynecology*, 2005, 105(2):383–9.

336. Seema, Patwari AK, Satyanarayana L. Relactation: an effective intervention to promote exclusive breastfeeding. *Journal of Tropical Pediatrics*, 1997, 43(4):213–6.

337. Kauppila A, Kivinen S, Ylikorkala O. A dose response relation between improved lactation and metoclopramide. *Lancet*, 1981, 1(8231):1175–7.

338. Weichert CE. Prolactin cycling and the management of breast-feeding failure. *Advances in Pediatrics*, 1980, 27:391–407.

339. Mathur GP et al. Lactation failure. *Indian Pediatrics*, 1992, 29(12):1541–4.

340. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *British Medical Journal*, 1988, 297:1304–1308.

341. Duvanel CB et al. Long term effects of neonatal hypoglycaemia on brain growth and psychomotor development in small for gestational age preterm infants. *Journal of Pediatrics*, 1999, 134:492–8.

342. Pildes RS et al. A prospective controlled study of neonatal hypoglycemia. *Pediatrics*, 1974, 54:5–14.

343. Brown JK, Cockburn F, Forfar JO. Clinical and chemical correlates in convulsions of the newborn. *Lancet*, 1972, 1(7742):135–9.

344. Cornblath M, Schwartz R. Outcome of neonatal hypoglycaemia. Complete data are needed (author's reply). *British Medical Journal*, 1999, 318(7177):194–5.

345. World Health Organization. *Hypoglycaemia of the Newborn: review of the literature*. Geneva, World Health Organization, 1997.

346. Cornblath M et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics*, 2000, 105(5):1141–5.

347. United States Public Health Service Health Resources Administration. *NCHS growth charts*. Rockville, MD, 1976 (HRA 76–1120, 25, 3).

348. de Onis M. The WHO Multicentre Growth Reference Study: planning, study design, and methodology. *Food and Nutrition Bulletin*, 2004, 25(1):S15–26.

349. Milner RD, Richards B. An analysis of birth weight by gestational age of infants born in England and Wales, 1967 to 1971. *Journal of Obstetrics & Gynaecology of the British Commonwealth*, 1974, 81(12):956–967.

350. Brenner WE, Edelman DA, Hendricks CH. A standard of fetal growth for the United States of America. *American Journal of Obstetrics and Gynecology*, 1976, 126:555–564.

351. Williams RL et al. Fetal growth and perinatal viability in California. *Obstetrics and Gynaecology*, 1982, 59:624–32.

352. Arbuckle TE, Wilkins R, Sherman GJ. Birth weight percentiles by gestational age in Canada. *Obstetrics and Gynaecology*, 1993, 81:39–48

353. Freeman JV et al. Cross sectional stature and weight reference curves for the UK, 1990. *Archives of Disease in Childhood*, 1995, 73(1):17–24.

354. Alexander GR et al. A United States national reference for fetal growth. *Obstetrics and Gynaecology*, 1996, 87:163–8.

355. Thomas P et al. A New Look at Intrauterine Growth and the Impact of Race, Altitude, and Gender. *Pediatrics*, 2000, 106(2):e21.

356. Kramer MS et al. A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics*, 2001, 108:1–7.

357. Lubchenco LO et al. Intrauterine growth as estimated from liveborn birth-weight data at 24 to 42 weeks of gestation. *Pediatrics*, 1963, 32:793–800.

358. Thomson AM, Billewicz WZ, Hytten FE. The assessment of fetal growth. *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1968, 75:903–916.

359. Williams AF. Low birthweight infants. In: Mclaren DS et al, eds. *Textbook of paediatric nutrition*. Edinburgh, Churchill Livingstone, 1991, 75–103.

360. Ehrenkranz RA et al. Longitudinal growth of hospitalized very low birth weight infants. *Pediatrics*, 1999, 104(2 Pt 1):280–9.

361. de Onis M, Garza C, Habicht JP. Time for a new growth reference. *Pediatrics*, 1997, 100(5):E8

362. Dewey KG et al. Growth of breast-fed and formula-fed infants from 0 to 18 months: the DARLING Study. *Pediatrics*, 1992, 89(6 Pt 1):1035–41.

363. Leroy V et al. International multicentre pooled analysis of late postnatal mother-to-child transmission of HIV-1 infection: Ghent International Working Group on Mother-to-Child Transmission of HIV. *Lancet*, 1998, 352(9128):597–600.

364. Cock KM, Weiss HA. The global epidemiology of HIV/AIDS. *Tropical Medicine and International Health*, 2000, 5(7):A3–9.

365. Landesman SH, Burns D. Quantifying HIV. *Journal of American Medical Association*, 1996, 275(8):640–1.

366. Fawzi W et al. Predictors of intrauterine and intrapartum transmission of HIV-1 among Tanzanian women. *AIDS*, 2001, 15(9):1157–65.

367. Coutsoudis A et al. Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. South African Vitamin A Study Group. *Lancet*, 1999 Aug 7;354(9177):471–6.

368. Tess BH et al. Infant feeding and risk of mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil. Sao Paulo Collaborative Study for Vertical Transmission of HIV-1. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*, 1998, 19(2):189–94.

369. Iliff PJ et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. *AIDS*, 2005, 19(7):699–708.

370. Chisenga M et al. Factors affecting the duration of exclusive breastfeeding among HIV-infected and -uninfected women in Lusaka, Zambia. *Journal of Human Lactation*, 2005, 21(3):266–75.

371. Coutsoudis A. Infant feeding dilemmas created by HIV: South African experiences. *Journal of Nutrition*, 2005, 135(4):956–9.

372. Israel-Ballard KA et al. Acceptability of heat treating breast milk to prevent mother-to-child transmission of human immunodeficiency virus in Zimbabwe: a qualitative study. *Journal of Human Lactation*, 2006, 22(1):48–60.

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