Neonatal intensive care 3

Advances in nutrition of the newborn infant

Jane E Harding, Barbara E Cormack, Tanith Alexander, Jane M Alsweiler, Frank H Bloomfield

Lancet 2017; 389: 1660–68

See **Editorial** page 1582

This is the third in a **Series** of three papers about neonatal intensive care

Liggins Institute (Prof J E Harding DPhil, B E Cormack MHSc, T Alexander MSc, J M Alsweiler PhD, F H Bloomfield PhD) **and Department of Paediatrics, Child and Youth Health** (J M Alsweiler)**, University of Auckland, Auckland, New Zealand; Newborn Services, Auckland City Hospital, Auckland, New Zealand** (B E Cormack)**; Neonatal Unit, Middlemore Hospital, Auckland, New Zealand** (T Alexander)

Correspondence to: Prof Jane E Harding, Liggins Institute, University of Auckland, Auckland 1023, New Zealand **j.harding@auckland.ac.nz**

Nutrition of newborn infants, particularly of those born preterm, has advanced substantially in recent years. Extremely preterm infants have high nutrient demands that are challenging to meet, such that growth faltering is common. Inadequate growth is associated with poor neurodevelopmental outcomes, and although improved early growth is associated with better cognitive outcomes, there might be a trade-off in terms of worse metabolic outcomes, although the contribution of early nutrition to these associations is not established. New developments include recommendations to increase protein supply, improve formulations of parenteral lipids, and provide mineral supplements while encouraging human milk feeding. However, high quality evidence of the risks and benefits of these developments is lacking. Clinical trials are also needed to assess the effect on preterm infants of experiencing the smell and taste of milk, to determine whether boys and girls should be fed differently, and to test effects of insulin and IGF-1 supplements on growth and developmental outcomes. Moderate-to-late preterm infants have neonatal nutritional challenges that are similar to those infants born at earlier gestations, but even less high quality evidence exists upon which to base clinical decisions. The focus of research in nutrition of infants born at term is largely directed at new formula products that will improve cognitive and metabolic outcomes. Providing the most effective nutrition to preterm infants should be prioritised as an important focus of neonatal care research to improve long-term metabolic and developmental outcomes.

Introduction

Nutrition of newborn infants has been the subject of debate and experimentation since antiquity. However, the focus of most recent research has been on the nutrition of preterm infants (less than 37 weeks' gestation). In this Series paper, we focus on advances and controversies in the nutrition of preterm infants and mention only briefly some aspects of nutrition of infants born at term (37–42 weeks' gestation) that pose challenges to clinicians and families. Some current practice points are drawn from the available evidence (panel).

Overview of issues for very preterm infants

Extremely preterm infants (less than 28 weeks' gestation) are born at a time when, if still in utero, they would be growing very rapidly.[1] To match fetal growth, an infant born at 24 weeks' gestation needs to double its weight by 30 weeks' postmenstrual age and be more than five times its birthweight by 40 weeks. This phenomenal growth demands a much higher intake of energy, protein, and other nutrients than is needed by infants born at later gestations. Extremely preterm infants are also born with low stores of key nutrients such as iron, zinc, calcium, and vitamins and with little or no subcutaneous fat and glycogen stores because most placental transfer of nutrients to provide these stores occurs in the third trimester of pregnancy.

The physiological immaturity of extremely preterm infants also makes provision of adequate nutrition a major challenge. Imbalances of fluid, glucose, and electrolytes are common in the first few days while an

Key messages

- Preterm birth is a nutritional emergency
- Breastmilk is the optimal food for all infants and is commonly supplemented to sustain growth in very preterm infants
- Rapid early growth is associated with improved cognitive outcomes in infants born preterm at the expense of adverse metabolic outcomes; optimal nutrition at early stages may ameliorate this trade-off
- The objective of neonatal nutritional strategies should be to optimise neurodevelopmental outcomes rather than growth alone
- However, there are insufficient high quality data to be confident of optimal macronutrient intakes for preterm infants
- There is a dearth of high quality evidence about the best approaches to feeding moderate-to-late preterm infants

Panel: Practice points for nutrition of very preterm infants

- Start parenteral nutrition, including aminoacids and lipids, within the first 24 h after birth
- Consider parenteral nutrition starter solutions with high nutrient concentration to provide nutrition while limiting early fluid intake
- Aim for aminoacid intakes of 3·5 g/kg per day
- Breastmilk is best for all infants but breastmilk alone might not support recommended growth trajectories
- Assessment of growth should include length, head circumference, and weight
- Nutritional intakes should be calculated using a standardised nutritional composition reference
- Supplements after discharge from hospital can accelerate growth in the first year after birth, but there is no evidence of improved later cognitive or metabolic outcomes

immature skin barrier, together with the demands of thermoregulation, respiratory distress, and other early illnesses, contribute to high energy and fluid requirements. However, early intake of large amounts of fluid can be associated with increased risk of adverse outcomes such as bronchopulmonary dysplasia and necrotising enterocolitis.[2] Structural and functional immaturity of the gut mean that enteral feeds are initially poorly tolerated, and immature coordination of sucking, swallowing, and breathing commonly prevents sucking feeds until close to term-equivalent age.

In practice, the usual approach is to initiate intravenous fluids immediately after birth and to provide parenteral nutrition until full enteral feeds are tolerated. Enteral feeds are begun as very small volumes (often 1 mL every 4–12 h) via an oro-gastric or naso-gastric tube. Volumes are increased slowly, with some clinicians providing only minimal enteral nutrition for several days before progressive increases in volume, despite lack of evidence that delaying progression improves outcome.[3] The transition from mainly intravenous nutrition to full enteral feeds can be episodic, with many reversals when feeds are not tolerated, and can take 7–14 days or more. If feeding is primarily with breastmilk, commercially available powdered or liquid milk fortifiers are often added to increase energy, protein, and micronutrient content that will support the infant's rapid growth, although there is no evidence of any long-term benefit.[4] Preterm formula preparations are often used for the same reason. Enteral tube feeding continues until the infant is mature enough to start sucking and can coordinate swallowing and breathing at around 32–34 weeks' post-menstrual age and continues to support feeding until full sucking feeds are established.

Breastmilk

Breastmilk is widely recognised as the best source of nutrition for preterm infants.[5] Mothers who deliver preterm produce breastmilk of different composition from those who deliver at term, with higher protein concentrations.[6] The advantages of feeding preterm infants breastmilk include improved immune defences and gastrointestinal function, a 58% reduction in the incidence of necrotising enterocolitis,[7] and improved long-term neurodevelopment outcomes.[8,9] These advantages have led to the establishment of breastmilk banks to provide donor human milk when a mother's own breastmilk is not available. However, donor milk usually comes from mothers late in lactation who delivered at term, and pasteurisation and storage result in variable nutrient loss, particularly of fat.[10] These concerns are partly addressed by the addition of fortifiers, which can include bovine or human milk proteins. There may be short-term advantages of feeding extremely preterm infants exclusively human milk (ie, including donor milk and human milk fortifier) as opposed to exclusively bovine milk products or a mother's own milk supplemented with a bovine-derived fortifier.[11] For example, a reduced incidence of necrotising enterocolitis was reported in two small trials.[12] In these trials, growth was slower in infants who were fed exclusively human milk, and there is still no evidence regarding the effect of feeding exclusively human milk on long-term growth, metabolic, or cognitive outcomes.

Challenges of volume and metabolic regulation

Adequate nutrition is essential for good growth in preterm infants, but the smaller the infant, the greater the challenge in providing optimal early nutrition.

Appropriate administration of intravenous nutrition is difficult, particularly in the first few days after birth. Infusion of drugs, maintenance of vascular access, and volume boluses to support blood pressure commonly result in administration of relatively large volumes of non-nutritional fluids. Findings from a systematic review[2] of five randomised trials of restricted versus liberal fluid intakes showed that fluid restriction reduces the risk of patent ductus arteriosus and necrotising enterocolitis, with non-significant trends towards reduction in risk of bronchopulmonary dysplasia, intracranial haemorrhage, and death. Thus, limits to both the volume and concentration of intravenous and enteral solutions that are tolerated in the first few days after birth mean that early growth failure is common.[13] Highly concentrated parenteral nutrition starter solutions can assist in achieving greater nutrient intakes in smaller fluid volumes during the first few critical days after birth.[14]

In the absence of level 1 evidence, international consensus guidelines are frequently used to guide practice, but recommended intakes are seldom achieved.[15] Despite evidence that 2–3 g/kg per day of both aminoacids and lipid can be administered safely on the day of birth,[16] surveys of practice in Europe and the USA show that only 38% of neonatal units gave the recommended protein intake on the day of birth, and only 40% of neonatal units gave lipid by day 3.[17] Thus, in the critical first 2 weeks after birth, preterm infants are commonly receiving less than 30–50% of the estimated nutritional intake that they would be receiving in utero. One reason is a well founded lack of confidence that the guidelines are evidence-based. However, given the physical and nutritional status of small infants, extremely preterm birth has been described as a nutritional emergency, and optimised nutrition should be a priority.[18] The oft-cited concern that intakes of large amounts of protein early after birth can have adverse metabolic and cognitive consequences comes from old studies in which the patient demographics and both intravenous and enteral nutrition solutions differed substantially from those used today.[15,19]

In addition to faltering postnatal growth, inadequate nutrition can contribute to electrolyte disturbances as cellular catabolism leads to the release of ions, such as phosphate and potassium, from cells. When nutrition is

later restored, the reverse effect on electrolyte balance can occur as restoration of anabolism leads to the cellular uptake of these ions. These electrolyte disturbances can be analogous to the refeeding syndrome described in malnourished adults.[20]

Although early intravenous nutrition for very preterm infants has become standard care, many uncertainties persist about the ideal quantity and balance of individual aminoacids, the optimal content of lipid emulsions, and optimal macronutrient intake at initiation of intravenous nutrition, and about how quickly glucose, protein, and lipid intake can be increased in the first few days after birth.

Mineral intake

Preterm infants are at risk of metabolic bone disease, which is characterised by bone demineralisation due to low mineral stores at birth, limited mineral intake, use of drugs that are deleterious to the skeleton (such as loop diuretics and corticosteroids), and, in some cases, vitamin D deficiency.[21] In severe cases, clinical rickets can ensue, and fractures can occur with minimal or no trauma in the smallest infants.

In the past, poor mineral solubility has restricted the amount of calcium and phosphorus added to parenteral nutrition solutions. However, the availability of organic phosphate has improved the stability of solutions containing high concentrations of calcium and organic phosphate, such that recommended parenteral intakes of calcium and phosphate can be achieved.[22]

Although breastmilk is considered the ideal nutrition for preterm infants, it does not contain sufficient minerals for the rapid bone growth that is necessary in preterm infants, and inadequate calcium and phosphate intakes in infants fed exclusively human milk can contribute to metabolic bone disease. Fortification of human milk with calcium, phosphate, and vitamin D is recommended,[21] although there is little reliable evidence that fortifcation has long-term benefit.[23]

Protein intake

The amount of protein intake needed to sustain normal growth varies according to the child's growth rate and, therefore, postconceptional age. Both empirical methods (observing the effect of manipulating macronutrient intakes on growth) and factorial methods (calculating requirements based on fetal accretion of body components) estimate that aminoacid intakes of at least 3–3·5 g/kg per day are necessary in babies with extremely low birthweight to achieve nitrogen retention and growth rates similar to the fetus in utero.[24] Findings from multiple studies have shown that early administration of intravenous aminoacid up to 3·6 g/kg per day is safe, well tolerated, and results in positive nitrogen balance and an improved rate of protein synthesis.[16]

However, results of randomised trials[25] to test the effect of intravenous intake of large amounts of protein on growth are inconclusive, with no studies powered adequately to assess later outcomes, including neurodevelopment. Results of the two most recent trials[26,27] showed opposite effects of high protein intake on head growth and no effect on body composition. Most of the studies are small (n≤150 participants), and protein intakes did not reach target levels, meaning the difference in protein intake between the control and intervention groups was much smaller than intended.

Similarly, there are few data on neurodevelopmental outcomes after high enteral protein intakes, although results of a meta-analysis[28] showed that measures of growth, including linear growth, were improved in infants with low birthweight (less than 2·5 kg) who were fed formula with high protein content. The substantial variation in the methods used to calculate nutritional intakes and growth makes comparisons between published datasets difficult and meta-analyses unreliable. Standardised reporting of neonatal nutrition and growth outcomes is now recommended (StRoNNG checklist).[29]

New intravenous lipid formulations

Energy intake in the first week after birth is greatly affected by intake of lipid because of its high energy content per unit volume. Delayed administration of lipid can also lead to essential fatty acid deficiency.[30] Increased cumulative intake of lipids during the first 2 weeks after birth has been associated with improved neurodevelopment at 1 year corrected age.[31] Traditional soybean-based lipid emulsions can contribute to increased levels of proinflammatory cytokines and oxidative stress in newborn infants.[32] New lipid emulsions containing fish, olive, and coconut oils provide a balanced ratio of omega-6 and and omega-3 polyunsaturated fatty acids and may be beneficial for preterm infants,[33] but more evidence is needed before their routine use can be recommended.

Glucose homeostasis

Preterm infants are at risk of hypoglycaemia because of limited glycogen and fat stores and impaired regulation of the glucose–insulin axis. This risk can continue for several weeks after birth, even after full enteral feeds are established.[34] Since glucose is the major cerebral fuel for newborn babies, insufficient brain glucose supply can contribute to brain injury. Early reports of a strong association between repeated blood glucose concentrations less than 2·6 mmol/L and later developmental impairment in very preterm infants[35] have not been replicated,[36] and there is little evidence that intervening to maintain normoglycaemia will improve outcomes. Nevertheless, neonatal hypoglycaemia is reported to be the only independent risk factor for adverse developmental outcome in late preterm infants.[37]

Intravenous nutrition usually delivers glucose at a high rate, and preterm infants do not consistently respond with

the normal suppression of endogenous glucose production.[38] These infants also have small volumes of insulin-sensitive tissues (fat and muscle) and limited insulin secretory capacity.[39] These factors combine to make hyperglycaemia common, with incidence as high as 80% in very preterm infants.[40]

High glucose infusion rates in extremely preterm infants are associated with an increased incidence of neonatal hyperglycaemia and death.[41] Hyperglycaemia is also associated with adverse outcomes including mortality, retinopathy of prematurity, and intraventricular haemorrhage.[42] Whether hyperglycaemia per se is the cause of adverse clinical outcomes or is simply a marker of the smallest and sickest infants remains uncertain, although results from studies in animals suggest that the relationship could be causal.[43] It is also uncertain how hyperglycaemia should be treated, or whether the commonly used treatment options (decreasing the intravenous glucose load or administering insulin) alter short-term or long-term outcomes.[44] Increasing protein intake while reducing glucose intake can reduce the incidence of hyperglycaemia,[45] as does increasing the amount of intravenous lipid.[46] However, reducing glucose intake too far might increase the risk of hypoglycaemia and inadequate calorie intake, leading to faltering growth. Early elective insulin treatment of extremely preterm infants has been shown to reduce the incidence of hyperglycaemia but not improve clinical outcomes.[47] Insulin treatment of infants with hyperglycaemia reduced blood glucose concentrations and improved early weight gain.[48] However, in both studies, insulin treatment was found to increase the risk of hypoglycaemia,[48,49] which might in turn increase the risk of long-term neurodevelopmental impairment.[35]

Smell and taste

The role of smell and taste in nutritional support of preterm infants has received little attention, despite the presence of functional taste receptors from 18 weeks' gestation and flavour perception from around 24 weeks' gestation.[49] Smell and taste are important for efficient metabolism as they activate the cephalic phase response and the release of appetite hormones in saliva.[50] Smell and taste also initiate metabolic processes through secretion of hormones such as insulin and ghrelin.[51] In adults, impaired oral nutrient sensing is associated with increased energy intake and body-mass index (BMI).[52] Preterm infants receive milk via a gastric tube, with no opportunity for smell or taste. However, changes in brain tissue oxygenation in response to odours have been detected in infants born as early as 32 weeks' gestation, with differential responses to odours rated as pleasant or unpleasant.[53] Some preliminary data indicate that provision of smell and taste before gastric tube feeds can decrease the time to reach full enteral feeds and full sucking feeds, reducing length of hospital stay.[54,55] Whether such a simple intervention improves feed tolerance, growth, and metabolic health in extremely preterm infants merits further research.

Long-term outcomes and current controversies

Trade-offs in metabolism and cognition

Preterm birth confers increased risk of adverse long-term health outcomes, including obesity, hypertension, and diabetes, as early as the third and fourth decades of life.[56,57] This metabolic risk is substantially related to increased adiposity. In a study of late preterm infants, a 182% increase in fat mass was recorded between birth and term-corrected age, by which time they had about 50% greater body fat than term-born controls.[58] This appears to be due to preserved development of fat mass but impaired accretion of lean mass, particularly in boys, and has been attributed to inadequate nutrient intake between birth and term-corrected age.[59]

Results of studies in immature infants (mean of 30 weeks' gestation) suggested that cognitive outcomes could be improved through enhanced nutrition with an enriched preterm formula.[60] However, infants who were fed the enriched formula also had increased adiposity and markers of insulin resistance in childhood.[61,62] In a more recent cohort of moderate-late preterm infants, enhanced growth in infancy was associated with improved cognition but poor metabolic outcomes at 8 years; an increase in weight gain of one standard deviation between birth and 4 months of age was associated with a 20% reduction in the risk of low IQ but a 27% increase in the risk of overweight or obesity.[63] These effects persisted through to 18 years of age. Data such as these suggest that there might be a trade-off in preterm infants receiving enhanced nutrition to prevent postnatal growth faltering; although enhanced nutrition results in better brain growth and cognitive outcomes, it accelerates weight gain and increases risk of metabolic and cardiovascular disease later in life. However, the causal relationships are not well established, and it is possible that they reflect, in part, healthy babies tolerating early and improved nutrition and having good long-term outcomes. Indeed, infants fed exclusively human milk have less pronounced weight gain than infants fed formula but have better cognitive outcomes (the so-called breastfeeding paradox).[64] Thus, infant growth, at least when assessed exclusively by weight rather than by overall growth, which would include assessment of length and head growth, has limitations as a measure of the effect of nutritional interventions, and much effort is being directed to identify early biomarkers of important later functional outcomes.[19]

Sex effects

Although girls and boys have long been known to grow differently, experience different metabolic and endocrine environments, and have different cognitive and health outcomes, little attention has been paid to the potential to improve outcomes after preterm birth by feeding girls and boys differently. It is well established that perinatal insults

can result in different adult phenotypes in males and females. In animal studies of perinatal insults in a variety of species, males are more likely than females to exhibit adverse effects in later life, such as impaired renal function, hypertension, insulin resistance, altered hypothalamic–pituitary–adrenal axis function, and altered growth.[65] The reasons for this sex-specific difference in susceptibility to early environmental perturbations are not well understood, but might include faster growth and hence greater substrate demands in males than in females, altered speed of maturation, different exposure to sex steroids, and sex-specific epigenetic mechanisms.[65] Unfortunately, findings from most clinical studies are not reported by sex, and most studies are not adequately powered to do so. Nevertheless, there is limited evidence that breastmilk composition varies according to the sex of the offspring, lending biological plausibility to the proposal that nutritional needs might be different in girls and boys.[66]

Of the few studies of early nutrition in preterm infants that do report outcomes for boys and girls separately, boys given nutritional supplements were found to have faster early growth, higher lean mass, and better neurodevelopmental outcomes than the boys who did not receive nutritional supplements. However, these benefits were not seen in girls who received the supplements. Rather, girls who received supplements were more likely to have increased adiposity and worse neurodevelopment than those who did not receive nutritional supplements.[8,67–69] This differential pattern of nutritional effects on boys and girls was also reported in preterm infants who were given preterm formula after discharge from hospital[70,71] as well as in infants born at term but small for gestational age who were given enriched formula for the first 6 months.[62,72] Future clinical trials of nutritional interventions need to be adequately powered to assess nutritional effects on boys and girls separately, detect sex-related interactions, and determine long-term metabolic and cardiovascular outcomes, body composition, and neurodevelopment.

Role of insulin and IGF-1

Insulin and IGF-1 have important roles in fetal growth and are both regulated by nutrition, particularly by the supply of glucose and aminoacids.[73] Fetal insulin deficiency, such as in pancreatic agenesis or after experimental pancreatectomy,[74] results in fetal growth restriction. Similarly, homozygous nonsense mutation of the human insulin receptor gene results in leprechaunism, with severe intrauterine growth restriction and postnatal growth failure,[75] and deletion of either the *Igf-1* or *Igf-2* genes in mice retards fetal growth.[76] In fetal lambs, insulin replacement after pancreatectomy restored fetal growth, but additional insulin above normal concentrations did not further increase growth.[74] Thus, insulin is necessary for normal fetal growth, but nutritional supply is also important.

The effect of insulin as a growth hormone decreases during the neonatal period, although the timing of this transition is less clear for very preterm infants, and IGF-1 has a key role in postnatal growth as the mediator of growth hormone-mediated somatic growth.[77] *Igf-1* knockout mice have poor postnatal and fetal growth,[78] and children with homozygous partial *IGF-1* deletion have poor growth and developmental delay.[79]

Plasma IGF-1 concentrations in very preterm infants are much lower than in the fetus at the equivalent gestational age.[79,80] This difference might reflect the absence of amniotic fluid containing IGF-1 swallowed by the fetus or postnatal nutritional limitations, including reduced protein intake.[81] Low plasma IGF-1 concentrations in extremely preterm infants have been associated with poor postnatal growth, neurodevelopmental impairment, and retinopathy of prematurity.[82,83] Plasma IGF-1 concentrations are also reduced by dexamethasone treatment in preterm infants, with negative effects on growth.[84]

These findings have led to attempts to increase circulating insulin and IGF-1 concentrations to improve postnatal growth in very preterm infants. Plasma IGF-1 concentrations are increased by early elective insulin treatment in infants with very low birthweight[85] but not by tight glycaemic control with insulin in preterm infants with hyperglycaemia.[47] A continuous infusion of IGF-1 and IGFBP-3 in extremely preterm infants is safe in the short term,[86] but additional research is needed to determine neonatal outcomes and long-term safety.

Nutritional supplements after discharge from hospital

Many infants have large deficits in growth and body composition and are still feeding poorly when discharged from hospital. Thus there has been considerable interest in investigating whether these infants should continue to receive nutritional supplementation after discharge.

Limited evidence from randomised trials suggests that preterm formula (increased concentrations of protein, energy, and multiple micronutrients), but not postdischarge formula (smaller increases in energy and protein, with variable micronutrients), improves growth in infants aged 12–18 months, with greater weight, body length, and head circumference, compared with infants who received standard formula. However, there is no evidence of improved developmental outcomes and no reports of later metabolic outcomes.[87] Similarly, the limited evidence[87] that is available suggests that addition of fortifier after discharge from hospital for breastfed infants does not improve growth or developmental outcome at 18 months.

Moderate-to-late preterm infants

Infants born at 32^{+0}–36^{+6} weeks' gestation account for more than 80% of preterm infants worldwide, totalling about 13 million infants per year.[88] These infants therefore constitute a much larger proportion of the health-care burden related to preterm birth than do extremely preterm infants. Most of these infants who are born in developed countries survive, but there is

increasing evidence that developmental and metabolic outcomes are impaired compared to those born at term.[89] At 34 weeks' gestation, the overall brain weight is 65% of the brain weight at 40 weeks' gestation,[90] so early nutrition to support brain growth is critical in these infants, as it is in those born more preterm. Furthermore, the apparent trade-off between metabolic and cognitive outcomes is seen in moderate-to-late preterm infants, not just those born very early.[63]

Moderate-to-late preterm infants have nutritional challenges after birth that are similar to those born extremely preterm. Their sucking, swallowing, breathing coordination, and gut motility are immature, supply of breastmilk is often delayed, and hepatic glycogen stores, which double is size between 36 weeks' and 40 weeks' gestation, are insufficient to compensate for a lack of enteral nutrition.

However, by contrast with very preterm infants, moderate-to-late preterm infants are often not given supplemental nutrition until full enteral feeds with breastmilk are established. Practice around their early nutritional support varies widely, reflecting a lack of evidence.[91] There are no data in support of supplementing with donor or formula milk early after birth, or whether to wait until the mother's breastmilk is available. There are also no data that show whether 10% dextrose alone is sufficient while waiting for the mother's milk or for enteral feeds to be tolerated, despite the inevitable accumulating nitrogen deficit, or whether infants should receive parenteral nutrition to reduce catabolism. All of these approaches are common in clinical practice. Adequately powered randomised trials are urgently needed to inform the optimal approach to feeding moderate-to-late preterm infants.

One of the challenges in providing nutrition of moderate-to-late preterm infants, and potentially one of the reasons that variation in practice is so wide and high quality evidence is so scarce, is that many of these infants can look and behave superficially similar to infants born at term. There is, therefore, often pressure to avoid medicalisation of late preterm infants who are otherwise well, and parents and carers sometimes have strong views about feeding. For example, some parents and carers would rather give infant formula by gastric tube to avoid intravenous infusion, whereas others would rather the infant received intravenous fluids while awaiting mother's milk to avoid formula. There is no reliable evidence to inform such decisions.

Infants born at term

Breastfeeding is undoubtedly the best nutrition for infants.[92] Breastfed infants have a reduced incidence of infectious diseases, including gastrointestinal and respiratory infections.[93] Breastfeeding also reduces the risk of otitis media, atopic eczema, sudden unexpected death in infancy, and, possibly, allergic rhinitis in childhood.[92,93] However, by contrast with observational data, long-term follow-up data from the PROBIT randomised trial[94,95] did not show any effect of breastfeeding on BMI, asthma, allergy, or mortality in mid-childhood. There is no evidence of a protective effect of breastfeeding on blood pressure or insulin resistance.[96]

Breastfeeding is biologically possible for most women and infants. However, in some rare situations, breastfeeding is either not possible or risks harming the infant. Maternal HIV is a relative contraindication to breastfeeding (when replacement feeding is acceptable, feasible, affordable, sustainable, and safe).[97] Some maternal medications, such as antineoplastics, can also be transmitted through breastmilk in concentrations that are dangerous to the infant. Rare metabolic diseases, such as galactosaemia, necessitate feeding with a specific formula to avoid potentially fatal complications.

Infant formulas are designed to mimic breastmilk as closely as possible. Research has been done to identify various nutrient additives for infant formulas such as low glycaemic carbohydrates, which had no beneficial effect on glycaemia.[98] The evidence of the benefits of supplementary long-chain polyunsaturated fatty acids is heterogeneous, with no clear benefit for growth, cognitive, or visual outcomes in infants born either at term or preterm, although there seems to be a reduced risk of allergy in later life.[99] This observation is supported by evidence of a nutrient–gene interaction, with most marked benefit in children who have the *FADS* genotype (fatty acid desaturase gene),[100] which causes low synthesis of long-chain polyunsaturated fatty acids from endogenous precursors.

Altering the macronutrient composition of formula has been shown to confer a large effect on metabolic outcomes. In a large randomised controlled trial[101] with babies born at term who were fed infant formula and follow-on formula with either a lower protein content (1·77 g protein/100 Kcal and 2·2 g protein/100 Kcal, respectively, ie, closer to the composition of breastmilk) or a high protein content (2·9 g protein/100 Kcal and 4·4 g protein/100 Kcal, respectively), weight-for-length *Z* score at 2 years of age was greatest in the group of infants that received formula with high protein content, translating into a higher BMI and 2·4-fold increased risk of obesity at 6 years of age.[102] The increased fat mass was visceral, rather than subcutaneous, indicating that there might be metabolic consequences as these children age.[103] Importantly, children who received the formula with low protein content as infants showed no decrement in mental performance at 8 years of age and performed similarly to children who were not randomised and were breastfed.[104]

Findings from experimental studies[105] in mice have shown that reformulating milk substitute so that the lipids are contained in larger droplets more analogous to those seen in breastmilk, rather than the small lipid droplets characteristic of formula milks, reduced fat accumulation by 30% and prevented the adult obesity associated with a post-weaning, western-style diet. The

modified formula was also found to improve performance in short-term memory tasks.[106]

Similarly, modifying triacylglycerol structure in formula to more closely resemble that in human milk might have benefits. Triacylglycerol is a major source of energy in both breastmilk and formula. About 25% of the fatty acids are palmitate, predominantly (70%) in the middle (sn-2) position on the glycerol backbone. In cow's milk and in formula, palmitate predominates in the sn-1 and sn-3 positions, where it is hydrolysed by pancreatic lipase. A formula containing a synthetic triacylglycerol with 50% of the palmitate in the sn-2 position resulted in softer stool (harder stools are more common in formula-fed infants), increased faecal bifidobacteria, and increased whole-body bone mineral content.[107]

All of these studies suggest that formula composition can be modified in ways that can improve metabolic outcomes, although breastfeeding, whenever possible, remains the optimal approach to nutrition of the newborn baby.

Conclusions and future directions

Although much has been learned about neonatal nutrition, there is much still to do, as clearly set out in the Pre-B Project.[10,19] Advances in nutrition of infants of all gestational ages will necessitate continual assessment of long-term metabolic and neurodevelopmental outcomes as well as of short-term effects on growth and body composition.

Contributors

All authors have contributed to drafting the manuscript and have reviewed the final version of this paper.

Declaration of interests

We declare no competing interests.

Acknowledgments

This work was funded in part by the Health Research Council of New Zealand and the New Zealand Lottery Grants Board. The funders have had no role in the writing of this paper or the decision to submit the paper for publication.

References

1 Villar J, Giuliani F, Fenton TR, et al. INTERGROWTH-21st very preterm size at birth reference charts. *Lancet* 2016; **387:** 844–45.

2 Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2014; **12:** CD000503.

3 Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent ecrotising enterocolitis in very low birth weight infants. *Cochrane Database Syst Rev* 2014; **12:** CD001970.

4 Brown JV, Embleton ND, Harding JE, McGuire W. Multi-nutrient fortification of human milk for preterm infants. *Cochrane Database Syst Rev* 2016; **5:** CD000343.

5 Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2010; **50:** 85–91.

6 Bauer J, Gerss J. Longitudinal analysis of macronutrients and minerals in human milk produced by mothers of preterm infants. *Clin Nutr* 2011; **30:** 215–20.

7 Ip S, Chung M, Raman G, et al. Breastfeeding and maternal and infant health outcomes in developed countries. *Evid Rep Technol Assess* 2007; **153:** 1–186.

8 Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. *BMJ* 1998; **317:** 1481–87.

9 Isaacs EB, Fischl BR, Quinn BT, Chong WK, Gadian DG, Lucas A. Impact of breast milk on intelligence quotient, brain size, and white matter development. *Pediatr Res* 2010; **67:** 357–62.

10 Raiten DJ, Steiber AL, Hand RK. Executive summary: evaluation of the evidence to support practice guidelines for nutritional care of preterm infants-the Pre-B Project. *Am J Clin Nutr 2016*; **103:** 599S–605S.

11 Sullivan S, Schanler RJ, Kim JH, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. *J Pediatr* 2010; **156:** 562–67 e1.

12 Cristofalo EA, Schanler RJ, Blanco CL, et al. Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. *J Pediatr* 2013; **163:** 1592–95 e1.

13 Ng DV, Brennan-Donnan J, Unger S, et al. How close are we to achieving energy and nutrient goals for very low birth weight infants in the first week? *JPEN* 2015; published online July 9. DOI:10.1177/0148607115594674.

14 Cormack BE, Bloomfield FH. Increased protein intake decreases postnatal growth faltering in ELBW babies. *Arch Dis Child Fetal Neonatal Ed* 2013; **98:** F399–404.10.

15 Koletzko B, Goulet O, Hunt J, et al. Guidelines on paediatric parenteral nutrition of the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) supported by the European Society of Paediatric Research *J Pediatr Gastroenterol Nutr* 2005; **41** (suppl 2): S1–87.

16 Vlaardingerbroek H, Vermeulen MJ, Rook D, et al. Safety and efficacy of early parenteral lipid and high-dose amino acid administration to very low birth weight infants. *J Pediatr* 2013; **163:** 638–44 e1–5.

17 Lapillonne A, Kermorvant-Duchemin E. A systematic review of practice surveys on parenteral nutrition for preterm infants. *J Nutr* 2013; **143:** 2061S–65S.

18 Corpeleijn WE, Vermeulen MJ, van den Akker CH, van Goudoever JB. Feeding very-low-birth-weight infants: our aspirations versus the reality in practice. *Ann Nutr Metab* 2011; **58** (suppl 1): 20–29.

19 Raiten DJ, Steiber AL, Carlson SE, et al. Working group reports: evaluation of the evidence to support practice guidelines for nutritional care of preterm infants-the Pre-B Project. *Am J Clin Nutr* 2016; **103:** 648S–78S.

20 Bonsante F, Iacobelli S, Latorre G, et al. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants—it is time to change the composition of the early parenteral nutrition. *PLoS One* 2013; **8:** e72880.

21 Mimouni FB, Mandel D, Lubetsky R, Senterre T. Calcium, phosphorus, magnesium and vitamin D requirements of the preterm infant. In: Koletzko B, ed. Nutritional care of preterm infants: scientific basis and practical guidelines. Basel: S. Karger AG, 2014: 140–51.

22 Ribeiro Dde O, Lobo BW, Volpato NM, da Veiga VF, Cabral LM, de Sousa VP. Influence of the calcium concentration in the presence of organic phosphorus on the physicochemical compatibility and stability of all-in-one admixtures for neonatal use. *Nutr J* 2009; **8:** 51.

23 Brown JV, Embleton ND, Harding JE, McGuire W. Multi-nutrient fortification of human milk for preterm infants. *Cochrane Database Syst Rev* 2016; **5:** CD000343.

24 Ziegler EE. Meeting the nutritional needs of the low-birth-weight infant. *Ann Nutr Metab* 2011; **58** (suppl 1): 8–18.

25 Osborn DA, Bolisetty S, Jones LJ, Sinn JKH. Systematic review of higher versus lower amino acid intake in parenteral nutrition for newborn infants. *J Paediatr Child Health* 2016; **52** (suppl 2): 58.

26 Uthaya S, Liu X, Babalis D, et al. Nutritional evaluation and optimisation in neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition. *Am J Clin Nutr* 2016; **103:** 1443–52.

27 Morgan C, McGowan P, Herwitker S, Hart AE, Turner MA. Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study. *Pediatrics* 2014; **133:** e120–28.

28 Fenton TR, Premji SS, Al-Wassia H, Sauve RS. Higher versus lower protein intake in formula-fed low birth weight infants. *Cochrane Database Syst Rev* 2014; **4:** CD003959.

29 Cormack BE, Embleton ND, van Goudoever JB, Hay WW Jr, Bloomfield FH. Comparing apples with apples: it is time for standardized reporting of neonatal nutrition and growth studies. *Pediatr Res* 2016; **79:** 810–20.

30 Lapillonne A, Eleni dit Trolli S, Kermorvant-Duchemin E. Postnatal docosahexaenoic acid deficiency is an inevitable consequence of current recommendations and practice in preterm infants. *Neonatology* 2010; **98:** 397–403.

31 dit Trolli SE, Kermorvant-Duchemin E, Huon C, Bremond-Gignac D, Lapillonne A. Early lipid supply and neurological development at one year in very low birth weight (VLBW) preterm infants. *Early Hum Dev* 2012; **88** (suppl 1)**:** S25–29.

32 Waitzberg DL, Torrinhas RS, Jacintho TM. New parenteral lipid emulsions for clinical use. *JPEN* 2006; **30:** 351–67.

33 Kapoor V, Glover R, Malviya MN. Alternative lipid emulsions versus pure soy oil based lipid emulsions for parenterally fed preterm infants. *Cochrane Database Syst Rev* 2015; **12:** CD009172.

34 Mola-Schenzle E, Staffler A, Klemme M, et al. Clinically stable very low birthweight infants are at risk for recurrent tissue glucose fluctuations even after fully established enteral nutrition. *Arch Dis Child Fetal Neonatal Ed* 2015; **100:** F126–31.

35 Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ* 1988; **297:** 1304–08.

36 Tin W, Brunskill G, Kelly T, Fritz S. 15-year follow-up of recurrent "hypoglycemia" in preterm infants. *Pediatrics* 2012; **130:** e1497–503.

37 Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, Reijneveld SA, Bos AF. Neonatal morbidities and developmental delay in moderately preterm-born children. *Pediatrics* 2012; **130:** e265–72.

38 Sunehag A, Gustafsson J, Ewald U. Very immature infants (< or = 30 Wk) respond to glucose infusion with incomplete suppression of glucose production. *Pediatr Res* 1994; **36:** 550–55.

39 Mitanchez-Mokhtari D, Lahlou N, Kieffer F, Magny JF, Roger M, Voyer M. Both relative insulin resistance and defective islet beta-cell processing of proinsulin are responsible for transient hyperglycemia in extremely preterm infants. *Pediatrics* 2004; **113:** 537–41.

40 Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, et al. Prevalence and determinants of hyperglycemia in very low birth weight infants: cohort analyses of the NIRTURE study. *J Pediatr* 2010; **157:** 715–19 e1–3.

41 Stensvold HJ, Strommen K, Lang AM, et al. Early enhanced parenteral nutrition, hyperglycemia, and death among extremely low-birth-weight infants. *JAMA Pediatr* 2015; **169:** 1003–10.

42 Alexandrou G, Skiold B, Karlen J, et al. Early hyperglycemia is a risk factor for death and white matter reduction in preterm infants. *Pediatrics* 2010; **125:** e584–e91.

43 Alsweiler JM, Harding JE, Bloomfield FH. Neonatal hyperglycaemia increases mortality and morbidity in preterm lambs. *Neonatology* 2013; **103:** 83–90.

44 Bottino M, Cowett RM, Sinclair JC. Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. *Cochrane Database Syst Rev* 2011; **10:** CD007453.

45 Alsweiler JM, Weston AF, Bloomfield FH. The effect of a change in parenteral nutrition on the incidence of neonatal hyperglycaemia. *J Paediatr Child Health* 2010; **46** (suppl 1)**:** 28.

46 Drenckpohl D, McConnell C, Gaffney S, Niehaus M, Macwan KS. Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life. *Pediatrics* 2008; **122**: 743–51.

47 Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, et al. Early insulin therapy in very-low-birth-weight infants. *N Engl J Med* 2008; **359:** 1873–84.

48 Alsweiler JM, Harding JE, Bloomfield FH. Tight glycemic control with insulin in hyperglycemic preterm babies: a randomized controlled trial. *Pediatrics* 2012; **129:** 639–47.

49 Lipchock SV, Reed DR, Mennella JA. The gustatory and olfactory systems during infancy: implications for development of feeding behaviors in the high-risk neonate. *Clin Perinatol* 2011; **38:** 627–41.

50 Zolotukhin S. Metabolic hormones in saliva: origins and functions. *Oral Dis* 2013; **19:** 219–29.

51 Teff KL. How neural mediation of anticipatory and compensatory insulin release helps us tolerate food. *Physiol Behav* 2011; **103:** 44–50.

52 Stewart JE, Feinle-Bisset C, Golding M, Delahunty C, Clifton PM, Keast RS. Oral sensitivity to fatty acids, food consumption and BMI in human subjects. *Br J Nutr* 2010; **104:** 145–52.

53 Bartocci M, Winberg J, Ruggiero C, Bergqvist LL, Serra G, Lagercrantz H. Activation of olfactory cortex in newborn infants after odor stimulation: a functional near-infrared spectroscopy study. *Pediatr Res* 2000; **48:** 18–23.

54 Yildiz A, Arikan D, Gozum S, Tastekin A, Budancamanak I. The effect of the odor of breast milk on the time needed for transition from gavage to total oral feeding in preterm infants. *J Nurs Scholarsh* 2011; **43:** 265–73.

55 Beker F, Opie G, Noble E, Jian Y, Bloomfield FH. Smell and taste to improve nutrition in very preterm infants: a randomized controlled pilot trial. *Neonatology* 2017; **111:** 260–66.

56 Crump C, Winkleby MA, Sundquist K, Sundquist J. Risk of hypertension among young adults who were born preterm: a Swedish national study of 636 000 births. *Am J Epidemiol* 2011; **173:** 797–803.

57 Crump C, Winkleby MA, Sundquist K, Sundquist J. Risk of diabetes among young adults born preterm in Sweden. *Diabetes Care* 2011; **34:** 1109–13.

58 Johnson MJ, Wootton SA, Leaf AA, Jackson AA. Preterm birth and body composition at term equivalent age: a systematic review and meta-analysis. *Pediatrics* 2012; **130:** e640–49.

59 Simon L, Frondas-Chauty A, Senterre T, Flamant C, Darmaun D, Roze JC. Determinants of body composition in preterm infants at the time of hospital discharge. *Am J Clin Nutr* 2014; **100:** 98–104.

60 Lucas A, Morley R, Cole TJ, Gore SM. A randomised multicentre study of human milk versus formula and later development in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1994; **70:** F141–46.

61 Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. *Lancet* 2003; **361:** 1089–97.

62 Singhal A, Kennedy K, Lanigan J, et al. Nutrition in infancy and long-term risk of obesity: evidence from 2 randomized controlled trials. *Am J Clin Nutr* 2010; **92:** 1133–44.

63 Belfort MB, Gillman MW, Buka SL, Casey PH, McCormick MC. Preterm infant linear growth and adiposity gain: trade-offs for later weight status and intelligence quotient. *J Pediatr* 2013; **163:** 1564–69, e2.

64 Roze JC, Darmaun D, Boquien CY, et al. The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT. *BMJ Open* 2012; **2:** e000834.

65 Aiken CE, Ozanne SE. Sex differences in developmental programming models. *Reproduction* 2013; **145:** R1–13.

66 Stam J, Sauer PJ, Boehm G. Can we define an infant's need from the composition of human milk? *Am J Clin Nutr* 2013; **98:** 521S–28S.

67 Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. *Lancet* 2001; **357:** 413–19.

68 Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? *Circulation* 2004; **109:** 1108–13.

69 van den Akker CH, te Braake FW, Weisglas-Kuperus N, van Goudoever JB. Observational outcome results following a randomized controlled trial of early amino acid administration in preterm infants. *J Pediatr Gastroenterol Nutr* 2014; **59:** 714–19.

70 Cooke RJ, Embleton ND, Griffin IJ, Wells JC, McCormick KP. Feeding preterm infants after hospital discharge: growth and development at 18 months of age. *Pediatr Res* 2001; **49:** 719–22.

71 Cooke RJ, McCormick K, Griffin IJ, et al. Feeding preterm infants after hospital discharge: effect of diet on body composition. *Pediatr Res* 1999; **46:** 461–64.

72 Morley R, Fewtrell MS, Abbott RA, Stephenson T, MacFadyen U, Lucas A. 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:** 515–21.

73 Oliver MH, Harding JE, Breier BH, Gluckman PD. Fetal insulin-like growth factor (IGF)-I and IGF-II are regulated differently by glucose or insulin in the sheep fetus. *Reprod Fertil Dev* 1996; **8**(1)**:** 167–72.

74 Fowden AL, Hughes P, Comline RS. The effects of insulin on the growth rate of the sheep fetus during late gestation. *Q J Exp Physiol* 1989; **74:** 703–14.

75 Krook A, Brueton L, O'Rahilly S. Homozygous nonsense mutation in the insulin receptor gene in infant with leprechaunism. *Lancet* 1993; **342:** 277–78.

76 Fowden AL. The insulin-like growth factors and feto-placental growth. *Placenta* 2003; **24:** 803–12.

77 Yumani DFJ, Lafeber HN, van Weissenbruch MM. Dietary proteins and IGF I levels in preterm infants: determinants of growth, body composition, and neurodevelopment. *Pediatr Res* 2015; **77:** 156–63.

78 Wang J, Zhou J, Powell-Braxton L, Bondy C. Effects of Igf1 gene deletion on postnatal growth patterns. *Endocrinology* 1999; **140:** 3391–94.

79 Hellstrom A, Ley D, Hansen-Pupp I, et al. Insulin-like growth factor 1 has multisystem effects on foetal and preterm infant development. *Acta Paediatrica* 2016; **105:** 576–86.

80 Hansen-Pupp I, Hovel H, Hellstrom A, et al. Postnatal decrease in circulating insulin-like growth factor-I and low brain volumes in very preterm infants. *J Clin Endocrinol Metab* 2011; **96:** 1129–35.

81 Smith WJ, Underwood LE, Keyes L, Clemmons DR. Use of insulin-like growth factor I (IGF-I) and IGF-binding protein measurements to monitor feeding of premature infants. *J Clin Endocrinol Metab* 1997; **82:** 3982–88.

82 Hellstrom A, Engstrom E, Hard AL, et al. Postnatal serum insulin-like growth factor I deficiency is associated with retinopathy of prematurity and other complications of premature birth. *Pediatrics* 2003; **112:** 1016–20.

83 Hansen-Pupp I, Hovel H, Lofqvist C, et al. Circulatory insulin-like growth factor-I and brain volumes in relation to neurodevelopmental outcome in very preterm infants. *Pediatr Res* 2013; **74:** 564–69.

84 Bloomfield FH, Knight DB, Breier BH, Harding JE. Growth restriction in dexamethasone-treated preterm infants may be mediated by reduced IGF-I and IGFBP-3 plasma concentrations. *Clin Endocrinol* 2001; **54:** 235–42.

85 Beardsall K, Ogilvy-Stuart AL, Frystyk J, et al. Early elective insulin therapy can reduce hyperglycemia and increase insulin-like growth factor-I levels in very low birth weight infants. *J Pediatr* 2007; **151:** 611–17.

86 Ley D, Hansen-Pupp I, Niklasson A, et al. Longitudinal infusion of a complex of insulin-like growth factor-I and IGF-binding protein-3 in five preterm infants: pharmacokinetics and short-term safety. *Pediatr Res* 2013; **73:** 68–74.

87 Young L, Morgan J, McCormick FM, McGuire W. Nutrient-enriched formula versus standard term formula for preterm infants following hospital discharge. *Cochrane Database Syst Rev* 2012; **3:** CD004696.

88 Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012; **379:** 2162–72.

89 Blencowe H, Lee AC, Cousens S, et al. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. *Pediatr Res* 2013; **74** (suppl 1)**:** 17–34.

90 Kinney HC. The near-term (late preterm) human brain and risk for periventricular leukomalacia: a review. *Semin Perinatol* 2006; **30:** 81–88.

91 Blackwell MT, Eichenwald EC, McAlmon K, et al. Interneonatal intensive care unit variation in growth rates and feeding practices in healthy moderately premature infants. *J Perinatol* 2005; **25:** 478–85.

92 Victora CG, Bahl R, Barros AJ, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016; **387:** 475–90.

93 Kramer MS, Chalmers B, Hodnett ED, et al. Promotion of breastfeeding intervention trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA* 2001; **285:** 413–20.

94 Kramer MS, Matush L, Vanilovich I, et al. Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial. *BMJ* 2007; **335:** 815.

95 Kramer MS, Matush L, Vanilovich I, et al. Effects of prolonged and exclusive breastfeeding on child height, weight, adiposity, and blood pressure at age 6·5 y: evidence from a large randomized trial. *Am J Clin Nutr* 2007; **86:** 1717–21.

96 Martin RM, Patel R, Kramer MS, et al. Effects of promoting longer-term and exclusive breastfeeding on cardiometabolic risk factors at age 11·5 years: a cluster-randomized, controlled trial. *Circulation* 2014; **129:** 321–29.

97 WHO. Guidelines on HIV and infant feeding. Principles and recommendations for infant feeding in the context of HIV and a summary of evidence. 2010. http://www.who.int/maternal_child_adolescent/documents/9789241599535/en/ (accessed July 1. 2016).

98 Fleddermann M, Rauh-Pfeiffer A, Demmelmair H, Holdt L, Teupser D, Koletzko B. Effects of a follow-on formula containing isomaltulose (palatinose) on metabolic response, acceptance, tolerance and safety in infants: a randomized-controlled trial. *PLoS One* 2016; **11:** e0151614.

99 Koletzko B, Boey CC, Campoy C, et al. Current information and Asian perspectives on long-chain polyunsaturated fatty acids in pregnancy, lactation, and infancy: systematic review and practice recommendations from an early nutrition academy workshop. *Ann Nutr Metab* 2014; **65:** 49–80.

100 Morales E, Bustamante M, Gonzalez JR, et al. Genetic variants of the FADS gene cluster and ELOVL gene family, colostrums LC-PUFA levels, breastfeeding, and child cognition. *PLoS One* 2011; **6:** e17181.

101 Koletzko B, von Kries R, Closa R, et al. Lower protein in infant formula is associated with lower weight up to age 2 y: a randomized clinical trial. *Am J Clin Nutr* 2009; **89:** 1836–45.

102 Weber M, Grote V, Closa-Monasterolo R, et al. Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial. *Am J Clin Nutr* 2014; **99:** 1041–51.

103 Gruszfeld D, Weber M, Gradowska K, et al. Association of early protein intake and pre-peritoneal fat at five years of age: Follow-up of a randomized clinical trial. *Nutr Metab Cardiovasc Dis* 2016; **26:** 824–832.

104 Escribano J, Luque V, Canals-Sans J, et al. Mental performance in 8-year-old children fed reduced protein content formula during the 1st year of life: safety analysis of a randomised clinical trial. *Br J Nutr* 2016; **22:** 1–9.

105 Baars A, Oosting A, Engels E, et al. Milk fat globule membrane coating of large lipid droplets in the diet of young mice prevents body fat accumulation in adulthood. *Br J Nutr* 2016; **115:** 1930–37.

106 Schipper L, van Dijk G, Broersen LM, et al. A postnatal diet containing phospholipids, processed to yield large, phospholipid-coated lipid droplets, affects specific cognitive behaviors in healthy male mice. *J Nutr* 2016; **146:** 1155–61.

107 Yao M, Lien EL, Capeding MR, et al. Effects of term infant formulas containing high sn-2 palmitate with and without oligofructose on stool composition, stool characteristics, and bifidogenicity. *J Pediatr Gastroenterol Nutr* 2014; **59:** 440–48.