Meeting the nutritional needs of premature babies: their future is in our hands

ABSTRACT

The goals of early nutrition in preterm infants are to provide all the necessary vital nutrients, achieve extra-uterine growth rates similar to fetuses of the same gestational age, and support functional neurodevelopmental outcomes that are comparable to those of infants born at term. It is vital to provide nutrition that will maximally support brain growth and development, but over-feeding with accelerated growth, fat accumulation and long-term metabolic consequences should also be avoided.

Because the morbidity associated with prematurity increases nutritional and energetic demands, the basic approach is of providing early intensive nutrition. Protein is the main driving force for growth and brain development. Since deficits in protein occur from the first day of extra-uterine life, sufficient quantities of parenteral amino acids should be provided from the first hours of life. With protein and carbohydrates, enough energy should also be provided, via concomitant early administration of intravenous lipid emulsions. Early initiation of enteral feeding with advancement to full enteral nutrition is associated with better maturation of the gut and better neuro-developmental outcomes. Human milk is the best food for preterm babies, although enrichment may be needed.

Keywords: very-low-birth-weight preterm infants; premature babies; early nutrition; growth and development; protein; early parenteral nutrition; human milk; enteral nutrition.

Preterm infants' nutrition is a developing exciting field which involves optimizing, improving and enriching the infant's nutrient intake, thus supporting better growth and future neurodevelopmental outcomes. The importance of early intensive nutrition enriched in protein has recently been emphasized. This approach requires early provision of full balanced parenteral nutrition to very-low-birth-weight premature infants immediately after birth until full enteral feeding, preferably of fortified human breast milk, can be established.

The goals of preterm infants' nutrition

The rates of survival of preterm infants have increased significantly over the last decades, especially in very-low-birth-weight (<1500 g) infants. Nutrition has a significant role in the immediate care of such preterm babies as well as in influencing their future. The goal for nutritional support of the very-low-birth-weight infant is to achieve a postnatal growth rate that approximates intra-uterine growth of a normal fetus at the same gestational age (American Academy of Pediatrics Committee on Nutrition, 1985; McNelis et al, 2017). However, the aim of preterm infants' nutrition is not just to supply the essential nutrients, maintain adequate growth rate, and try to mimic the body composition of the same gestational age fetus, but also to achieve functional neurodevelopmental outcome comparable to that of an infant born at term (Ziegler, 2011; De Curtis and Rigo, 2012; Harding et al, 2017; McNelis et al, 2017).

Human growth is unique because the priority of human development is the brain, and thus providing nutrition that will enhance optimal development of the brain is of utmost importance. The brain grows and develops very quickly in the critical period of prematurity between 20 and 32 weeks of gestation (Colvin et al, 2004), and well beyond it into 34–36 weeks gestation, now termed as late prematurity (Kugelman and Colin, 2013). Any insult to brain development during this critical period, including morbidities, infections or undernutrition, has a major impact on later outcome especially in preterm infants (Colvin et al, 2004).

The current focus of nutritional science has shifted from meeting nutritional needs to determining the biological effects that nutrition has on immediate and lifetime health. In this respect the term programming is used to define any stimulus or insult during a critical or sensitive period of development that can have long-term or lifetime effects on an organism.

Nutrition in early life, especially in preterm infants, has major impacts on long-term health and development, especially on brain growth, cognitive function, linear growth and bone mineralization, but also on future health and risk of metabolic syndrome and cardiovascular disease in adult life (Lucas et al, 1997; Ehrenkranz et al, 2011; Lapillonne and Griffin, 2013; Harding et al, 2017). While restricted intake of nutrients with relatively slow growth might have some possible benefits for later cardiovascular outcome in low birth-weight infants, it carries the risks of under-nutrition and its adverse consequences, especially on the brain's size and cell number, which has profound adverse effects on later cognition, learning memory and behaviour (Bhatia, 2005). Thus, despite our concerns regarding future metabolic consequences in adult life, the current approach to nutritional support for premature infants, especially very-low-birth-weight extremely premature infants, is to try to avoid under-nutrition and extra-uterine growth restriction that could hamper

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their linear growth and mental development (Berry et al, 1997; Ehrenkranz et al, 1999; Embleton et al, 2001; De Curtis and Rigo, 2004; Ziegler, 2011; Harding et al, 2017; McNelis et al, 2017).

Early intensive nutrition

The accompanying morbidities associated with prematurity increase the nutritional and energetic needs of preterm infants, thus making this nutritional challenge even greater. This approach to early nutrition in preterm infants, aimed at maximizing growth and optimizing development, was originally termed early aggressive nutrition, and is now better termed as the early intensive nutritional approach (Embleton et al, 2001; Ehrenkranz, 2007; Stephens et al, 2009; Ziegler, 2011). This approach aims to minimize extra-uterine growth restriction by the early provision of full nutritional support immediately after birth, including all nutrients, in order to avoid the catabolic state resulting from disconnecting the newborn preterm infant from the placental supply of nutrients, and the comorbidities of prematurity, mainly respiratory distress syndrome (Wilson et al, 1997; Ziegler et al, 2002; Ehrenkranz, 2007; De Curtis and Rigo, 2012).

The challenge of supplying adequate nutrients to very-low-birth-weight infants is further complicated by gut immaturity, mandating complete parenteral nutrition from birth (Harding et al, 2017; McNelis et al, 2017) in most of these infants. This has now become the largest age group dependent on parenteral nutrition (Beecroft et al, 1999; Ziegler, 2011).

Protein: the driving force for growth and brain development

Protein is the major driving force for growth and brain development in preterm, especially very-low-birth-weight infants. Deficits and growth deficits start in the first days of life (Van Goudoever et al, 1995; te Braake et al, 2005). The association between protein (or amino acid) intake and nitrogen retention in the first days of life has been shown in multiple studies (Thureen et al, 2003; te Braake et al, 2005; Embleton, 2007).

The current recommendation is to provide at least 2.0-3.0 g/kg/day amino acids as soon as possible after birth in order to avoid tissue breakdown, and to aim for a daily intake of 3.5 g/kg/day (Harding et al, 2017) (even up to 4.0 g/kg/day in very premature, very-low-birth-weight infants) within the next 3–4 days (Riskin et al, 2015). Although associated with transient elevation of serum urea nitrogen levels, this increased protein intake is considered safe in very-low-birth-weight infants without acidosis or hyperammonaemia. It is associated with better nitrogen balance, better weight gain, less extra-uterine growth restriction, better clinical outcomes (e.g. decreased chronic lung disease, bronchopulmonary dysplasia), and improved developmental outcomes (Porcelli and Sisk, 2002; Thureen et al, 2003; Embleton, 2007; Stephens et al, 2009; Valentine et al, 2009; Riskin et al, 2015). Early administration of amino acids was also found to decrease the frequency and severity of hypoglycemic episodes in very-low-birth-weight preterm infants, possibly by stimulating endogenous secretion of insulin and insulin-

> “Both hypoglycaemia and hyperglycaemia have long-term effects on morbidity and mortality in preterm infants.”

like growth factors that also promote growth (De Curtis and Rigo, 2012). Further studies are needed regarding the optimal composition of parenteral amino acid solutions (Thureen et al, 2003; Blanco et al, 2011; McNelis et al, 2017).

The importance of full balanced nutrition with sufficient energy

Glucose

Early provision of glucose, which is the main energy source in fetal life (the placental infusion rate of glucose is approximately 5.5 mg/kg/minute, range 4–6 mg/kg/minute), is required in order to provide an immediate continuous energy source to the brain and vital organs, and maintain glucose homeostasis after birth (Mitanchez, 2007; McNelis et al, 2017). However, premature babies are at risk of abnormal glucose homeostasis during the first week of their life, which can either be hypoglycaemia because of limited glycogen and fat stores because of the short pregnancy (mainly lacking the third trimester), or hyperglycaemia, most probably the result of defective processing of proinsulin in beta cells within the Langerhans islets of the pancreas or the result of partial insulin resistance of target cells (Mitanchez, 2007; De Curtis and Rigo, 2012; McNelis et al, 2017).

Both hypoglycaemia and hyperglycaemia have long-term effects on morbidity and mortality in preterm infants (Heimann et al, 2007; Harding et al, 2017). While hypoglycaemia may require higher rates of glucose infusion (up to 8–10 mg/kg/minute), hyperglycaemia is mostly treated by lowering glucose infusion rates (as low as 3.5 mg/kg/minute), while providing alternative nutrients and fuels by giving complete parenteral nutrition (Sunehag et al, 1999; Sinclair et al, 2011; Riskin et al, 2015). This approach of providing lower glucose infusion levels as part of full early parenteral nutrition might be more successful than administration of insulin (Sinclair et al, 2011), probably as a result of the relative insulin resistance in very-low-birth-weight infants during the first week of life (De Curtis and Rigo, 2012).

Lipids

Along with protein and carbohydrates, preterm infants need energy, thus intravenous lipid emulsions should be an integral component of parenteral nutrition for very-low-birth-weight preterm infants. Very-low-birth-weight infants can handle protein intake of 2.4–3.6 g/kg/day as long as they are provided with enough energy for metabolism (Embleton, 2007). Studies have shown that many such very-low-birth-weight preterm infants are not given enough energy (te Braake et al, 2005, 2007), and only by adding lipid emulsions from the very first day of life (1–2 g/kg/day) can their requirements for energy be met (te Braake et al, 2007; Vlaardingerbroek et al, 2012; Riskin et al, 2015).

Lipid emulsions (at a daily dose of 3–3.5 g/kg/day) not only provide energy, but also provide essential fatty acids (especially soybean oil-based emulsions) of which preterm infants have low stores, as well as long chain polyunsaturated fatty acids, especially docosahexanoic acid, which is important for brain and retinal development. In recent years emulsions that are not purely soybean oil-based have been introduced, containing also medium-chain triglycerides, olive and/or fish oils. There are suggestions that the use of non-purely soybean oil-based lipid emulsions is associated with a reduced incidence of sepsis (Vlaardingerbroek et al, 2012) and might reduce the risk of parenteral nutrition-associated liver disease and cholestasis (Riskin et al, 2015; Harding et al, 2017).

It is very important to provide energy and protein in the right ratio in early parenteral nutrition during the first days of life (Embleton, 2007). The recommended ratio of protein to energy in parenteral nutrition is approximately 3.3 g protein/100 kcal (range: 2.7–3.9 g protein/100 kcal, higher at younger gestational ages and lower birth weights) (Ziegler, 2011; Riskin et al, 2015). The optimal protein:energy ratio can improve lipid tolerance, as measured by lower serum triglyceride levels, as well as amino acid tolerance as expressed by lower blood urea levels and reduced metabolic acidosis. Special attention should also be paid to the appropriate distribution of calories in preterm infants, so that 10–15% comes from protein, 30–40% from lipids and 45–55% from carbohydrates.

Enteral feeding – the importance of human breast milk for preterm infants

Parenteral nutrition provides energy and nutrients to the very-low-birth-weight preterm infant and prevents deficiency states and extra-uterine growth restriction until the infant can absorb enteral nutrition, which is preferable (especially for mineral absorption, i.e. calcium and phosphorus). Minimal trophic enteral feeding to prime the premature gut and prepare it for food absorption is recommended from the first days of life. This enteral feeding is gradually increased to full enteral feeding according to the general status of the baby, comorbidities and gut maturation.

Early initiation of enteral feeding with advancement to full enteral nutrition in preterm infants, including very-low-birth-weight infants, was associated with more rapid maturation of the gastrointestinal system, less feeding intolerance and better neurodevelopmental outcomes. These findings have led to the widely accepted recommendation for each neonatal intensive care unit to institute and optimize local guidelines for early initiation and advancement of enteral nutrition (McNelis et al, 2017) which could result in a decrease in the incidence of necrotizing enterocolitis (Patole and de Klerk, 2005).

Human breast milk – preferably the mother's own milk, but in recent years also available from donor milk banks – is the optimal nutrition for preterm infants who can enjoy its nutritional, immunological and developmental advantages (Riskin and Bader, 2003; Harding et al, 2017; McNelis et al, 2017). However, many infants will require enrichment of human milk by fortifiers, in order to meed the increased demands of preterm infants for protein and minerals (Riskin and Bader, 2003; Harding et al, 2017). **BJHM**

Conflict of interest: none.

KEY POINTS

- Nutrition in early life is important, not only for the growth of preterm infants but also for their development and health in later life.
- Morbidities associated with prematurity increase nutritional and energetic needs, thus requiring an intensive approach to providing early optimal nutrition to preterm infants to achieve the best possible growth and development. This is driven primarily by early protein intake.
- Early parenteral nutrition to provide sufficient intake of amino acids is recommended in very-low-birth-weight preterm infants in order to overcome protein deficit and negative nitrogen balance. Lipid emulsions should be added to early parenteral nutrition along with protein and carbohydrates to provide enough energy.
- Human milk is the best food for preterm babies. Its advantages are in host defence, nutritional components and suitability for gut absorption, as well as its psychological and developmental value. The limitations of human milk for preterm babies, mainly in its relatively low content of protein and minerals, can be compensated for by using human milk fortifiers.

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