Early Nutrition and Later Outcomes in Preterm Infants

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Abstract

The developmental origins of health and disease is an emerging area of interest that amalgamates many areas of scientific studies and encompasses a wide range of diverse disciplines from epidemiology to molecular biology. Evidence has accumulated to show that early life experiences, both in utero and in infancy have long-term effects on many body systems. There are now good data to show that suboptimal in utero growth, especially when combined with rapid growth acceleration in early postnatal life may increase the risk of later life metabolic disease. The mechanisms are complex but likely to involve epigenetic marks such as DNA methylation. Preterm infants frequently experience suboptimal nutrient intakes in early postnatal life and exhibit growth failure within the NICU. They also receive products that may not provide either an optimal quantity or quality of nutrients. Follow-up studies have now shown much higher risks for long-term chronic disease in children and adults who were born preterm. There are higher levels of insulin resistance and abnormal partitioning of fat deposition. The onset of puberty seems earlier, average height is less and blood pressure, measures of vascular health and lipid profiles suggest cardiovascular health is likely to differ from healthy term born controls. Despite this, there are no data to suggest an overall benefit of limiting nutrient intake, or restricting growth in preterm infants. There are strong data to show that the preterm brain is exquisitely vulnerable to undernutrition, and that suboptimal nutrient intakes may permanently affect later cognitive attainment. A clinical focus on early nutrient intakes and breast milk provision is key to optimising long-term health outcomes.

Over the last two decades a series of epidemiological studies have demonstrated close associations between birth weight and later cardiovascular health. These have been amalgamated under the term developmental origins of health and disease (DOHaD) [1]. It has been postulated that birth weight is reflective of foetal growth, and when combined with other measures of growth adequacy such as length to produce a ponderal index (or a measure of thinness), it could be used to infer a
causal relationship between in utero exposures (especially nutritional) and subsequent health and disease. In most studies, the data support the hypothesis of a causative relationship, although debates remain about the precise role of postnatal growth acceleration. Some argue that in the absence of rapid infant growth acceleration the adverse risks of slow in utero growth may be much less pronounced [2]. The term ‘programming’ has been suggested to describe the relationship between these early exposures and disease at a much later stage in the life course [3], whilst at the same recognising that the metabolic alterations themselves are likely to reflect evolved traits in animals that maximise survival and thereby the passage of genetic inheritance (as DNA) to the next generation.

Interest in the underpinning science and the public health implications of DOHaD have led to an explosion of research in this area. The majority of the work focuses on term populations, with some of the strongest data linking infants born growth-restricted to increased insulin resistance in later life. The worldwide epidemic of type 2 diabetes is not solely a feature of lifestyle but reflects how our evolutionary inheritance interacts with both the nutritional and physical environment and early life events. However, several authors have described the limitations of using auxological measures and indices (e.g. BMI) as biomarkers of foetal growth adequacy and the difficulties, for example, in making inferences about deposition of adipose tissue. The description of a ‘thin-fat’ baby has been used to exemplify this problem whereby apparently thin, growth restricted (‘IUGR’) term infants may actually have disproportionately high levels of intra-abdominal adipose tissue [4]. Several lines of enquiry suggest that rapid growth in otherwise healthy term infants might be disadvantageous for later metabolic health.

Whilst the molecular mechanisms that underpin the lifelong effects of early exposures remain to be determined in humans, there are now a wealth of data in animals to show proof-of-principle for many of these relationships and mechanisms. In fact, many of the first animal studies pre-date the explosion of epidemiologic studies that were initially referred to as the ‘Barker hypothesis’ before being more adequately described within the DOHaD umbrella. Combined together, these studies suggest there may be critical or sensitive windows in early life. The existing data suggest that early exposures result in dynamic effects across the life-course that may be due to epigenetic marks [5], and affect not only organ structure and function, but also endocrine and stress control systems.

It is less clear how the existing data can be extrapolated into determining optimal nutritional care for infants born preterm. Preterm delivery is increasingly prevalent and accounts for around 10% of all deliveries. Typical growth patterns of extremely preterm infants shows that many fail to grow adequately over the first few weeks [6]. Compared to longitudinal foetal growth centiles, the typical birth weight of preterm infants is less than the foetal 50th centile. This is because many are the result of a pregnancy compromised by placental dysfunction or maternal ill health such as obesity, gestational diabetes or malnutrition.
Low weight at birth is compounded by practical difficulties in providing adequate nutrient intakes over the first few days and weeks. The aetiology of inadequate nutrient provision is multi-factorial and includes practical aspects such as access to parental nutrition (PN), metabolic intolerance such as hyperglycaemia and fear of necrotising enterocolitis (NEC) that leads to a delay in establishing enteral feeds [7]. Suboptimal nutrient quality is also an issue. For example, current PN solutions represent a compromise between practical issues such as solubility and an uncertainty about the precise requirements for individual essential amino acids. Current intravenous lipid solutions are not designed to provide optimal nutrition for preterm infants and many contain inappropriate amounts and ratios of essential fatty acids.

Taking the DOHaD perspective, it is possible to view the period of care on a Neonatal Intensive Care Unit (NICU) as potentially providing an energy rich environment after an initial period of inadequate nutrition. This may appear analogous to term infants with IUGR who subsequently experience growth acceleration, but is of course happening at a different postconceptual time point. Most current infant formula and breast milk fortifiers provide inadequate protein:energy ratios for extremely preterm babies resulting in inappropriate growth either due to inadequate protein or excess energy intakes [8].

Despite potential concerns about long-term adverse metabolic consequences of catch-up growth in the NICU it is clear that this represents a different phenomenon to growth acceleration in term IUGR infants. In addition, data suggest that inadequate nutrition in early life may permanently affect brain outcomes [9, 10]. Whilst there may be a causal relationship between early nutrition and later metabolic and cardiovascular outcomes in preterm infants, the exquisite vulnerability of the preterm brain argue for immediate and continued nutrient intakes during NICU stay and in the postdischarge period.

In relation to other mammals, humans have evolved to have a large brain:body weight ratio, with a brain 10 times larger for body size than for many other mammals. Studies have also shown that around half of all energy expenditure in early infancy is accounted for by the brain. Length of gestation could be considered a compromise between the continuing safety and benefits offered by the in utero environment versus the demands placed on the placenta and the mother to meet such high nutrient requirements as the foetus grows in size. Humans are born at the optimal stage of brain maturity determined by evolutionary pressures, but would be considered immature compared to many other newborn mammals. The human brain exhibits a pattern of growth that is quite different to many other mammals including other primates. In most primates the fastest period of brain growth occurs prior to delivery, whereas in humans brain growth peaks at around term age. Approximately 80–90% of adult brain volume is accrued between 24 weeks’ gestation and 2 years of age, a period during which clinicians have a large degree of control over what nutrients the infant receives.
Brain development is of course far more complex than a simple acquisition of tissue volume. Several key neurological processes occur at overlapping stages meaning that insults (e.g., inadequate nutrition) at differing time points will result in differing effects [11]. Neuronal migration takes place from the early weeks but is largely complete by term, synaptogenesis occurs from the 2nd trimester through into childhood, and myelination spans the period from the 3rd trimester through until the 2nd or 3rd decade of life. It is easy to appreciate why nutrient restriction in what should have been the third trimester and in early infancy might have such long-lasting effects on cognition. Parallel with brain development are changes in every body organ and system occurring throughout foetal and infant life. Lack of key nutrients during these sensitive windows will result in later phenotypes that differ depending on the timing, severity and duration of the insult.

Numerous studies show relationships between poor growth in the NICU and worse neurodevelopmental outcome. In a study of extremely preterm infants Ehrenkranz et al. [12] showed that infants in the lowest quartiles of weight gain had significantly higher rates of neurodevelopmental impairment and cerebral palsy than infants in the highest quartile. In infants born <1,000 g, Stephens et al. [13] showed a striking relationship between energy and protein intakes in just the first week of life and neurodevelopmental outcome in infancy. Considered with other data, there is a strong argument that poor nutrient intake in the first days and weeks may result in impaired cognition later in life.

One of the challenges of interpreting observational data linking nutrient intakes to growth or neurological outcomes is the possibility of reverse causation. Despite the biological plausibility of a direct causal link, adjusting for confounders, whilst possible, may remain incomplete. There may be other independent factors (including genetic) affecting both growth and brain outcome. A direct causal link can only be determined using prospective controlled trials. To be able to identify the long-term metabolic and brain outcome such studies are necessarily complex and expensive and run the risk of increasing attritional losses over time [14]. Despite these problems, important data are now emerging.

In a series of landmark papers Lucas and coworkers [15–19] have demonstrated short- and long-term neurodevelopmental and cognitive benefits of enhanced early nutrition and breast milk in preterm infants. In addition, neuro-imaging using magnetic resonance imaging (MRI) has identified specific brain structures that appear particularly vulnerable to early nutrition [20, 21]. These studies have shown dramatic deficits in verbal intelligence quotient (IQ) in adolescence for those not receiving enhanced nutrient intakes that are themselves closely correlated with volume of the caudate nucleus on MRI [15]. This relationship has biologic plausibility. Inadequate nutrition, over a relatively short period on the NICU, results in highly significant and persisting disadvantages in cognition that may track throughout the life course.

The neurocognitive advantages of enhanced nutrient intake on the NICU appear clear, but there are no controlled studies demonstrating an advantage of enhanced nutrient intake in the immediate postdischarge period [22]. Brain growth and
development remains very active at this stage and brain energy requirements remain very high. There are data to suggest that at this stage preterm infants regulate their enteral intakes based on calories [23]. It seems plausible then that as long as infants feed on demand, the majority of otherwise well preterm infants may meet their caloric requirement if endocrine feedback mechanisms regulating hunger are intact. Protein and micronutrient intakes achieved in the postdischarge period are then a function of their ratio to caloric density, so whilst nutrient intakes and density remain important at that stage, the principal effects might be in determining growth and body composition, rather than a major effect on neurodevelopment.

However, some data do show relationships between nutrient intake and/or growth and neurodevelopment in the postdischarge period. In a study of relatively mature preterm infants (median gestation 34 weeks) faster weight gain was associated with higher IQ after adjustment for likely confounding variables that included gender, ethnicity, maternal education, income, IQ and smoking [24]. For each additional standard deviation score in weight gain there was an increase of 1.9 in the total IQ score (Wechsler Intelligence Scale for Children, III., USA).

Despite the importance of ensuring good nutrient intakes for brain development there are data to show that there are metabolic costs associated with preterm birth, and perhaps early enhanced nutrient intakes. Singhal et al. [25] have shown that preterm infants who received higher nutrient intakes over just the first 2 weeks had higher levels of 32–33 split pro-insulin (a measure of insulin resistance) in adolescence. There was also a stepwise relationship with quartiles of weight gain over the first 2 weeks and subsequent insulin levels. A further study in the same cohort demonstrated decreased levels of brachial artery flow-mediated endothelium-dependant dilatation (FMD), i.e. less good vascular ‘health’ in those with high weight gain compared to those with low weight gain [26]. Interestingly, FMD was similar in the high weight gain group to term controls. These findings, perhaps, should not be interpreted as a disadvantage of nutrient enrichment so much as a potential metabolic advantage of slower growth induced by nutrient restriction.

Several others have shown insulin resistance in later childhood in those born preterm, though not all studies are consistent [27]. In a large epidemiologic study based in Helsinki the risk of developing type 2 diabetes for adults born before 35 weeks gestation had an odds ratio of 1.59 [28]. Furthermore, there are good data to show that body composition in preterm infants is different. Using MRI, Uthaya et al. [29] have shown increased levels of intrahepatic lipid (strongly associated with insulin resistance when present in adults) and abnormal adipose tissue partitioning in preterm infants at a corrected age of term compared to healthy controls. Preterm infants had lower levels of subcutaneous fat but increased levels of intra-abdominal adipose tissue. Interestingly, there was limited association with nutritional factors but strong associations with degree of illness suggesting that stress, or an altered response to stress, may be the principal determinants of abnormal partitioning. Similar features have been seen in adults who were born preterm with increased total levels of intra-abdominal adipose
tissue, higher blood pressure and increased levels of intrahepatic and intramyocellular lipid [30]. There is also evidence of effects on control systems, with pubertal onset occurring perhaps 1–2 years earlier in children who were born preterm.

Mineral bone disease is prevalent amongst preterm infants on the NICU. Many receive inadequate mineral and vitamin D intakes, especially those who receive unfortified breast milk. Despite this, there are few data showing that mineral bone disease or prematurity results in significantly decreased bone mineral density (BMD) in later life. Whilst pre- and postdischarge nutrient enrichment results in higher BMD in some studies, it is not certain these effects persist. Follow-up in early adulthood suggested that the only key determinant of BMD might be breast milk exposure with increasing intakes associated with greater BMD, an effect largely explained by greater bone area [31]. This concurs with a multitude of other data suggesting that breast milk improves a range of long-term outcomes in preterm infants.

Although there may be a trade-off between optimising neurocognitive outcomes and increased metabolic problems in later life, the accumulating data continue to support a focus on nutrition in the NICU for infants born preterm. The mechanisms linking early life exposure to later phenotypes in humans are only starting to be explored, but new data are already emerging to show relationships between DNA methylation and later phenotype [5, 32, 33]. The existing data suggest that clinicians should commence early nutritional support (using PN where necessary) and seek to attain recommended intakes of all key nutrients from the first few days. Breast milk provision should be maximised and consideration given to appropriate fortification. Nutrition must remain a key focus of neonatal intensive care in the pre- and postdischarge period.

References


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