Is preterm nutrition a trade-off between head and heart?

Gopi Menon,†, 1 Angela L Davidson,1 Amanda Jane Drake,2 Nicholas D Embleton† 3

A regular subject of discussion on neonatal ward rounds is the rate of weight gain in preterm infants. This is because we believe that good nutrition is important for optimal body growth, including brain growth and development. In this issue, Andrews et al† demonstrate that it is possible to get close to what many consider the holy grail of preterm nutrition, which is matching the rate of fetal growth as displayed on the WHO preterm growth chart. In this article, we identify some of the difficulties with this concept and suggest priorities for research.

THE FETAL-NEONATAL TRANSITION IN PRETERM INFANTS

The third trimester of pregnancy is a period of rapid growth. Normal fetal physiology is abruptly challenged at the time of preterm delivery, by the difficulty in sustaining the rate of nutrient supply, and as a result of major changes in environment including: (1) air breathing and increased tissue oxygen availability; (2) milk feeding; and (3) bacterial colonisation. The physiological alterations, including major changes in gene expression resulting from adaptation to these new conditions, mean that the use of fetal growth as a standard for preterm infants, and assumptions about weight gain as a surrogate for the quality of neonatal tissue growth need to be considered carefully.

Very low birthweight preterm infants frequently develop an early fall-off in neonatal weight centile level (‘centile lag’) when assessed against a fetal growth standard and tend to occupy a lower weight centile at discharge than at birth. This is accompanied by a nutrient deficit when compared with the same period in fetal life. Much has been made of the correlation between a greater centile lag in the neonatal period and neurodevelopmental impairment despite the likelihood of residual confounding factors and the lack of data from intervention trials. This has encouraged the assumption that the greater the weight gain the better, and terms such as ‘growth failure’ and ‘undernutrition’ have become normalised in referring to the commonly seen centile fall-off. Although Andrews et al† suggest that poor early growth is not inevitable, it should be noted that: (A) the success in avoiding centile lag overall was achieved with inclusion of a substantial number of babies who were small for gestation at birth and showed centile catch-up, and (B) there were fall-offs in centile level for head circumference and length in many gestational groups. In the absence of any measurements of body composition in this study, this raises doubts about the quality of growth of the infants studied.

THE EX-PRETERM PHENOTYPE

One of the reasons why we have to reconsider our approach to preterm nutrition is the fact that preterm infants and other groups showing ‘centile lag’ followed by ‘catch up growth’ in infancy later show increased adiposity and early markers of increased risk of cardiovascular disease and diabetes—a phenomenon known as early life programming. There are several possible explanations for this ‘ex-preterm phenotype’ and it is worth exploring these in more detail in order to challenge our current approach to nutrition in the preterm and to help guide further research. Is the outcome the result of (A) early undernutrition being allowed, thus making catch-up growth inevitable, (B) the wrong target being set for preterm growth, or (C) an inevitable programming effect of preterm birth and the adaptation to it?

EARLY UNDERNUTRITION FOLLOWED BY CATCH-UP GROWTH

First, it could be that our inability to mimic normal intraterine nutrition coupled with catch-up growth leads to an increased risk of cardiometabolic disease (cardiometabolic programming). The time-honoured approach of the gradual introduction of parenteral nutrition, together with increased maternal and donor breast milk feeding and an inconsistent approach to human milk fortification may all contribute to the early centile lag that is prevalent in very preterm infants. Thus, in theory, preventing early centile lag through ‘aggressive nutrition’ could provide a solution by optimising brain growth and avoiding cardiometabolic programming. Although this sounds ideal, the optimal nature and timing of such an intervention is unclear. There is some evidence that rapid weight gain in early infancy (equivalent to the period to term-corrected age in preterm infants) is not associated with later adverse metabolic consequences, while rapid weight gain in later childhood is detrimental to cardiometabolic status.

THE WRONG TYPE OF GROWTH

Second, it could be our attempts to achieve close to intraterine growth rates, using the crude measure of weight gain and the equally crude nutritional interventions at our disposal, that are to blame for cardiometabolic programming. Preterm infants at term equivalent have a body composition which is very different from term-born infants, with less lean tissue and more adipose tissue. Could this be because we provide a suboptimal combination of nutrients? When compared with intraterine supply, the diets we provide are particularly low in protein. Glucose and amino acids are used as the main energy sources in fetal life, with a significant proportion of the amino acid intake being oxidised for energy. If the ambition is to match fetal nutrient intakes, the current approach often provides higher amounts of glucose and lipid and much lower amounts of protein.

It is possible that there is a ‘critical growth period’ during which a good nutrient intake will determine later body size and brain development. Early high-protein intake resulted in a much lower incidence of centile lag and better head growth in preterm infants. First week energy and protein intakes were associated with neurodevelopmental outcome. The justification for the slow introduction of amino acid solutions has been that preterm infants were considered to be in a catabolic state after birth, as evidenced by high urea levels, and were thus unable to process higher intakes. However, there is now evidence that increased protein intakes induce an anabolic response and promote a positive nitrogen balance, and it may thus be appropriate to encourage a higher amino acid intake. Fortified breast
milk also frequently falls short of recommended intakes of protein, and additional protein fortification has been proposed. It should be noted that preterm infants are a heterogeneous group differing by gestation, intrauterine growth attainment and illness severity, and thus a unified approach to nutrition might not be appropriate.

Defining the optimal approach to introducing and advancing enteral feeds is just as difficult. This is complicated by the desire, on the one hand, to achieve ‘good’ nutritional status and growth rates and on the other the anxiety about gut injury and necrotising enterocolitis. In this context, the evidence that preterm babies fed mainly breast milk do well from a neurodevelopmental perspective despite showing slower weight gain is noteworthy. The place of breast milk fortification remains uncertain with concern that fortifiers based on bovine protein in particular may increase the risk of gut injury.

PROGRAMMING EFFECT OF PRETERM BIRTH

Third, it could be that the preterm-at-term phenotype is simply the inevitable consequence of an endocrine and metabolic physiology that is fundamentally different from that of the fetus or term-born baby. It has, thus, been suggested that a preterm growth standard based on longitudinal measurements of postnatal growth in preterm infants should be used in preference to charts based on measurements of birth weights at different gestations although this is a hypothesis which requires testing. The process of birth, particularly in vaginal delivery, is associated with a stress response which affects gene expression and promotes an adaptive metabolic response enabling the term baby to use body stores via glycogenolysis and gluconeogenesis until breast milk is able to supply nutritional demands. This stress response may be exacerbated in the preterm infant by illness and by the use of drugs including steroids and inotropes. There is a strong association between illness severity and intra-abdominal adiposity in preterm infants at term. In term infants, the initiation of enteral feeds generates dramatic endocrine changes which facilitate the adaptation to an intermittent supply of nutrients via the gastrointestinal tract, and this may be disrupted following preterm delivery. Subsequently, the low levels of insulin-like growth factor-1, a major growth-promoting hormone in the neonatal period and an altered hypothalamo-pituitary adrenal axis resulting in relative cortisol deficiency may contribute to the later cardiometabolic disease risk. Finally, breast milk contains numerous hormones and growth factors, some of which almost certainly have systemic effects following absorption from the gut.

INTERVENTION TRIALS

There have been several trials of boosting early nutrient intake by means of parenteral nutrition in preterm infants, including two recent UK trials, nutritional evaluation and optimisation in neonates (NEON) and standardised, concentrated, additional macronutrients, parenteral nutrition in very preterm infants (SCAMP). It is clear that amino acids initiated as early as the first day of life can be used for tissue growth. However, there are no intervention trials with adequate power to determine long-term functional effects including cognition and metabolism. In the NEON trial, higher early amino acid intakes failed to improve lean body mass at term equivalent but were associated with poorer head growth. However, the NEON trial was not powered to look at brain outcomes and there were no group differences in brain volumes measured using MRI. In the SCAMP trial, in which lower amounts of amino acid were given in the first 3 days than in NEON, higher early amino acid intakes towards the end of the first week led to a larger head size at 28 days. Other trials have raised concerns about increased sepsis and worse neurodevelopment with high early amino acid intake—indeed a systematic review concluded that the relationship between increased early nutrition and neurodevelopmental outcomes is uncertain. Trials in term newborns and older children admitted to paediatric intensive care units have raised concerns that supply of amino acids in excess of metabolic capacity may cause harm.

SUGGESTIONS FOR FUTURE RESEARCH

The lack of progress in our understanding of nutritional interventions reflects in part the challenges of conducting adequately powered large-scale collaborative trials. Advancing our understanding of nutritional care of the preterm infant requires well-designed randomised controlled trials, with clarity about the intervention being tested and functional outcomes that are meaningful to children and families. In order to progress research, there is the urgent need to identify short-term markers predictive of important longer term outcomes. The Neonatal Nutrition Network in the UK has helped facilitate this through research collaboration having input into many of the recent large UK feeding trials. The paper by Andrews et al has shown that it is possible to implement a complex nutritional intervention. The challenges for researchers are: (A) to engage with the clinical community to identify areas of uncertainty where equipoise exists; (B) to identify early biomarkers of important long-term outcomes which can be used as primary outcomes in clinical trials; (C) to work with children and families to identify the outcomes of most importance to them; and (D) to work with the wider community to highlight the importance of early life nutrition and the need for greater research funding in this area.

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