Catch-up growth and the developmental origins of health in preterm infants

This article is intended as an overview of the developmental origins of health and disease hypothesis, and its application to growth in preterm infants, in particular the phenomenon of 'catch-up growth'.

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Key points

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1. The developmental origins of health and disease hypothesis emphasises the importance of early life nutrition in determining later metabolic outcomes.
2. Preterm infants are vulnerable to under nutrition in the neonatal unit and after discharge.
3. Increasing early nutrient intakes and promoting catch-up growth in preterm babies is associated with improved neurodevelopmental outcome.
4. Breast milk remains the most important intervention in infant feeding.

Survival rates for premature birth are improving worldwide, meaning a greater number of preterm babies are surviving into later life.[1] This has led to an increased focus on the long-term outcomes of prematurity. Preterm infants face significant nutritional challenges from birth through to the post-discharge period. They are also at risk of poorer neuro-developmental and growth outcomes. Concerns about the long-term effects of this have paralleled the growing recognition of the developmental origins of health and disease (DOHaD) hypothesis. This has highlighted the potential influence of the intrauterine and early life environments on later health outcomes, particularly the metabolic syndrome.

Optimal nutrition on the neonatal unit is important to maintain appropriate growth and to maximise cognitive outcome. However, immaturity and illness can be significant barriers to intake, with many infants acquiring a cumulative 'nutrient deficit'.[2] This initial growth failure means many preterm infants are discharged on a lower growth centile than at birth. Conversely, concerns about the effect of excessive postnatal nutrition on the programming of disease have arisen from studies showing poorer metabolic outcomes, especially in term-born low birthweight (LBW) infants. 'Catch-up growth' may modulate this early programming effect. Current findings in preterm infants suggest improving intake and catch-up growth both pre- and post-discharge is associated with improved neurodevelopmental outcomes.

The developmental origins of health and disease

The DOHaD concept originated from the work of Barker and his colleagues in the 1980s on low birth weight and later cardiovascular outcomes.[3] This built on previous animal studies where early nutrient exposures affected later growth potential.[4] Since then, the field has expanded to encompass a range of research disciplines, from the early epidemiological studies, to recent advances in the field of epigenetics. The DOHaD hypothesis emphasises that early life events, beginning in fetal life and continuing throughout infancy and even childhood, contribute to long-term adult health outcomes. It is classically described in relation to early nutrition and metabolic outcomes such as cardiovascular disease, type II diabetes and obesity. The greatest risks are to those infants born small for gestation who have poor growth *in utero* and experience rapid infant weight gain, although there may also be risks from poor infant growth followed by rapid childhood growth.[5] Other authors have incorporated evolutionary biology into the model, arguing that the degree of mismatch between the pre- and postnatal environments dictates the health outcome. This is explained by the predictive-adaptive

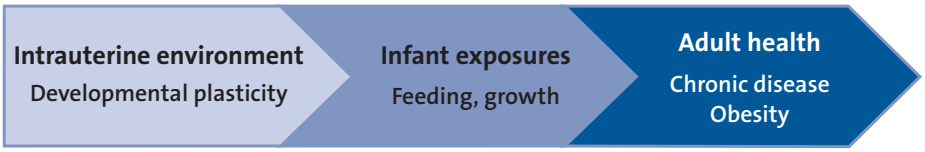

FIGURE 1 The DOHaD hypothesis.

response hypothesis, where cues in early life can influence expression of genes.[6] If the fetus is programmed by placental under-nutrition to expect a nutrient-scarce environment after birth, but receives the opposite, its phenotype is maladapted for this and adverse health outcomes may follow. The programming effects aim to maximise short-term survival to reproductive age, but increase the risk of non-communicable disease in the long term.[7] Other studies have related birth weight and early growth to a host of other indicators, such as bone density, body composition and blood pressure.

There is much debate as to the relative importance of such findings in relation to other 'life exposures' and environmental factors such as smoking and diet. However, these findings have been widely replicated and represent an important window of 'developmental plasticity'[8] for the infant (**FIGURE 1**). The DOHaD hypothesis is a fascinating example of the interaction between genes and the environment and emphasises the potential impact that healthcare professionals can have when instigating nutritional management. These findings, however, are mostly related to term infants; much less is known regarding the growth of premature infants. It is difficult to know what the term birth weight might have been in a preterm, potentially growth-restricted neonate; particularly if birth size primarily reflects the intrauterine environment, rather than genetic influence.[9] This has caused a dilemma in determining the most appropriate pre- and post-discharge nutrition for a preterm infant to maximise growth and development, while minimising potential metabolic consequences.

Nutritional vulnerability in the preterm infant

The potential for malnutrition in the preterm infant begins well before birth. A nutrient-scarce intrauterine environment (eg due to placental insufficiency) leads to poor fetal growth and in some cases results in preterm delivery. This presents the neonate with many challenges. In the late second and third trimester the fetal brain undergoes crucial maturation and increase in volume and is particularly vulnerable to white matter injury.[10] *Ex utero*, the preterm infant is exposed to a range of stresses and stimuli that it would not experience in the womb. It also faces the difficulties of breathing with immature lungs and digestion with an immature gut. Therefore it is not surprising that many preterm infants do not meet their daily nutritional requirements in the first few weeks of life.

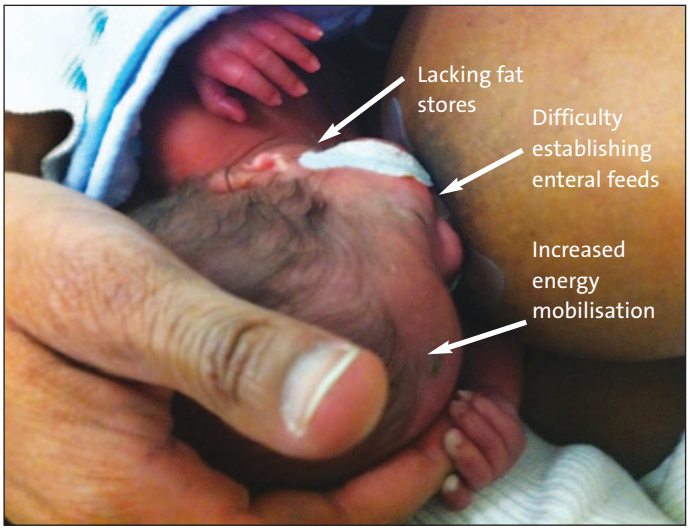

FIGURE 2 The contributing factors to nutrient deficit *in utero*. Image reprinted with the parents' permission.

The growth trajectory of the preterm infant is not straightforward. The initial physiological weight loss exhibited in healthy, full-term neonates is regarded as normal. However, the preterm infant may have limited fat storage and so requires more urgent nutritional attention. Using data from body composition studies, a 24-week preterm infant is composed of around 90% water; the remaining 10% is mostly protein.[11] In a tiny 500g baby, this would mean only 50g of tissue.[12] Thus, the infant has little or no energy stores to cope with the increased energy requirements of premature delivery. There may also be increased energy mobilisation due to stress or infection. After birth, there is often a delay in establishing feeding necessitating the use of parenteral nutrition (PN) while enteral feeds are gradually introduced. Enteral feeds can be stopped and restarted due to concerns of intolerance or the risk of necrotising enterocolitis. There are significant risks associated with PN such as infection, cholestasis and procedural risks of central line placement. All these difficulties mean that the infant is vulnerable to inadequate intake and growth failure, and a resulting nutrient deficit that accumulates over days (**FIGURE 2**).

Current recommendations of protein and lipid requirements are often not met in the neonatal intensive care unit. Research is ongoing to determine the most appropriate composition of these requirements, particularly in relation to protein-calorie ratios and their effect on growth and body composition.

Enteral nutrition faces its own challenges: breast milk and preterm formulas have different nutritional composition, and studies have suggested improved metabolic outcomes with breast milk.[13] This may be partly related to maternal behavioural effects on feeding practice. Given that it is very difficult to regulate volume intake with breastfeeding, the mother has to respond to infant cues of hunger and satiety.[14] Formula feeding may result in excess intake, due to the caregiver's ability to visually monitor volumes. This difference may also have a programming effect, indeed it has been suggested that hypothalamic neurons regulating intake show plasticity during lactation.[15] Despite lack of consensus about the effects of early intakes on later health, breast milk remains the most appropriate nutrition for preterm infants for cognitive and growth outcomes.

Catch-up growth

The phenomenon of catch-up growth describes an increased rate of weight or length gain after a period of growth restriction.[12] In premature infants, who have usually dropped below their birth centile, this is often seen following discharge on a high-nutrient formula. These babies demonstrate accelerated growth to regain their birth centile. The alternative 'growth acceleration' seen in term babies, that accelerate weight/length gain above their birth centile, occurs at a different developmental phase, as shown in **FIGURE 3**. This is more often seen in term babies who are formula fed rather than breastfed.

Formula has key differences in constituency to breast milk, particularly in the first few days of life when calorie intake from breast milk is low. Formula usually has higher levels of protein, which may drive growth through endocrine processes.[16] The long-term consequences of these differences are still unclear.

There is an important distinction between an 'appropriately grown' LBW preterm infant and an *in utero* growth-restricted LBW term infant. Of course, premature birth may be the result of a compromised pregnancy, and so the preterm baby may also show signs of intrauterine growth restriction (IUGR). Being 'appropriately small' or growth-restricted have different growth and metabolic sequelae, particularly if growth after birth is significantly different to growth *in utero*. This causes difficulties when monitoring and defining growth patterns; if birth centile is also affected by IUGR, it is difficult to know what the appropriate rate of growth is for the neonate. As stated in the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPHGAN) guidelines, a high degree of uncertainty remains.[17] Therefore, intrauterine references for growth and intake are considered the most useful estimates.

Studies on catch-up growth in preterm infants tend to use weight gain as an indicator of growth. It is important to recognise that growth and weight gain are not the same – a similar increase in 'weight' can represent very different alterations in body composition of fat and lean tissue. Studies of adolescents born preterm have shown decreased bone density, increased blood pressure, insulin resistance and abnormal fat deposition, although this is not consistent.[18] These adolescents also tend to be slightly smaller than their term-born counterparts. Outcomes such as these are important as potential surrogate markers for chronic disease. It is difficult to separate the poorer metabolic and skeletal growth outcomes of prematurity from those directly related to early growth and feeding. It is therefore unclear whether faster early growth causes problems because growth itself alters metabolism, or whether faster growth is simply a marker for increased intakes. Observational retrospective data cannot reliably separate these effects.

Large cohort studies demonstrate associations between excessive weight gain in infancy and higher fat mass, systolic blood pressure and insulin resistance in later life.[19,20] These findings in small for gestational age term babies have created somewhat negative connotations around the term 'catch-up growth', particularly in the context of increasing rates of childhood and adolescent obesity. As discussed, the difficulty in comparing term and preterm infants means that more studies relating nutrition and growth in preterm infants to later outcomes are needed.

Studies of preterm infants have linked metabolic outcomes with particular periods of growth. The findings of associations with altered insulin resistance and poorer vascular health appear to be limited to the first two weeks after birth.[21,22] Early nutrient intakes, specifically pre-discharge, may therefore be particularly important in determining any programming effect in preterm infants. It is also important to emphasise that long-term follow-up of trials of intake in early life in preterm infants demonstrate that increased intake results in better cognitive outcomes.[23] This evidence would strongly discourage nutrient restriction in early life. Arguably, cognitive outcome remains the key priority after premature birth.[24] Studies show that many preterm infants have impaired cognitive development, with a variety of longer-term effects including behavioural problems, mental illness and lower IQ compared to peers. There is currently insufficient evidence to suggest an appropriate rate of growth that both maximises neurodevelopment and minimises the risk of adverse metabolic outcomes. Catch-up growth in itself must not be viewed as detrimental but viewed in the wider context of optimising early infant health and neurodevelopment, and the ongoing nutritional continuum after discharge.

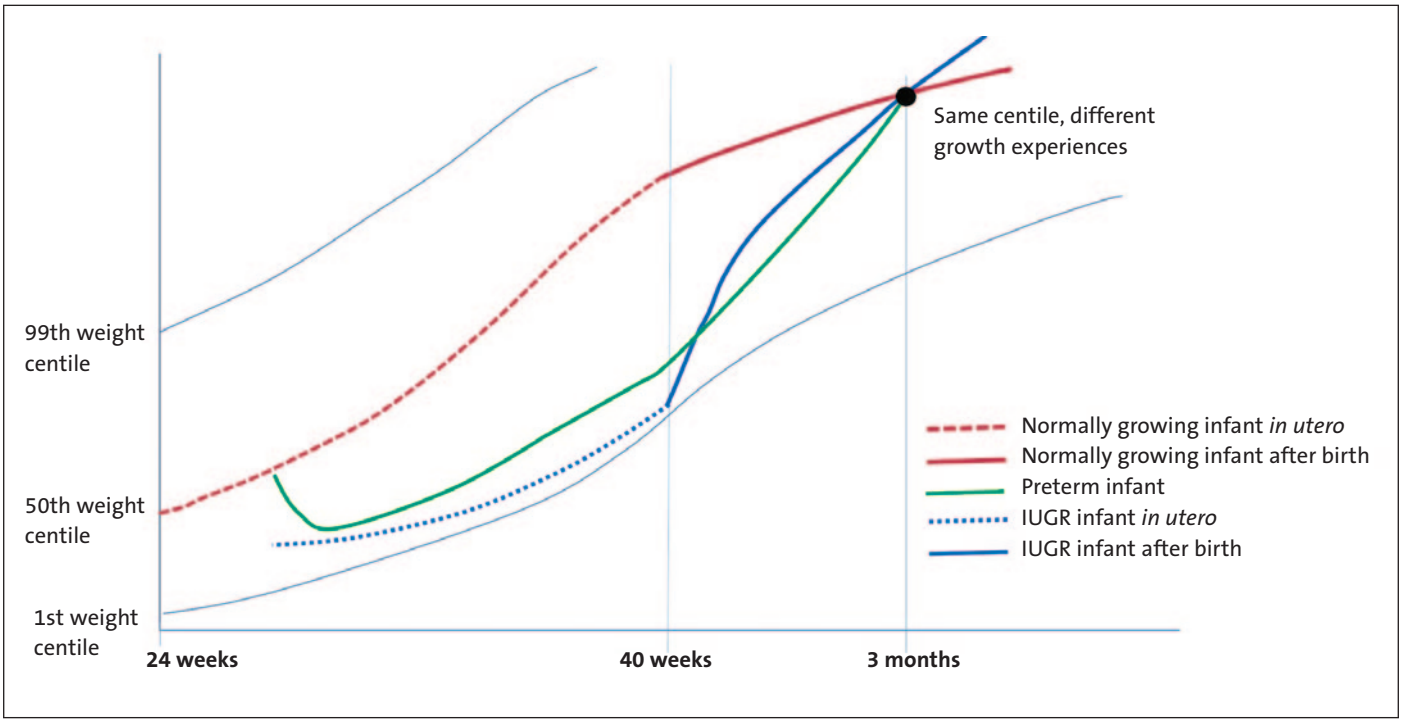

FIGURE 3 A representation of the differences in catch-up growth in growth-restricted term infants and 'appropriately small' preterm infants. Key: IUGR = intrauterine growth restriction.

Post-discharge nutrition

Most preterm infants are discharged around their corrected term gestation. Catch-up growth peaks around the corrected age of term and then shows a decline towards three months of age. Although the pre-discharge period seems to be the most critical in terms of catch-up growth, the need for continued nutritional management after discharge is also important, as shown by the logic model in **FIGURE 4**. Breastfeeding remains the primary recommendation for post-discharge feeding. If mothers choose to breastfeed, the infant will benefit from supplemental iron and vitamin D.[25] Alternatively, a preterm formula may be used, but there is no evidence to suggest a neurodevelopmental advantage to formula feeding.

Early protein intake has recently received increased attention. In term infants, excess protein intake and the resulting weight gain during infancy has been shown to increase obesity in later life.[26] However, in preterm infants a higher protein intake may not be disadvantageous, while even a small protein deficit limits growth.[17] Preterm infants have higher protein requirements for tissue synthesis and, as such, preterm formulas have a higher protein-calorie ratio than term formulas. A higher protein-energy ratio is associated with increased lean mass deposition while minimising inappropriate fat deposition. A study by Wilson et al[27] found that in addition to better growth outcomes, an aggressive nutritional approach did not cause an increased risk of adverse metabolic or clinical effects. Since fat requirements *ex utero* are greater than those *in utero*, it is difficult to quantify the appropriate percentage and distribution of fat mass in premature infants.

Conclusion

The DOHaD hypothesis has provided evidence for the importance of early nutritional exposures in determining later life health outcomes. This, compounded with the phenomenon of catch-up growth, points towards potential for modification of risk with appropriate nutritional management in neonates. However, results of nutritional exposures between term and preterm infants cannot be assumed to be equivalent and, as such, a different nutritional approach is required.

Efforts must be made to minimise the nutritional deficit in preterm babies. Existing evidence suggests a beneficial effect of optimal nutrition in preterm infants, particularly for neurodevelopmental outcome. Although this is the key priority, some consideration must be given to possible long-term effects of altered body composition and insulin sensitivity.

Observational data will never be free from the difficulty of adjusting for the many confounders in the maternal-infant-child health relationship, or separating growth from feeding. Breastfeeding remains the preferred source of nutritional intake for the preterm infant. The role of specialised formula in the absence of breast milk and its effects on catch-up growth need further clarification in long-term follow-up studies.

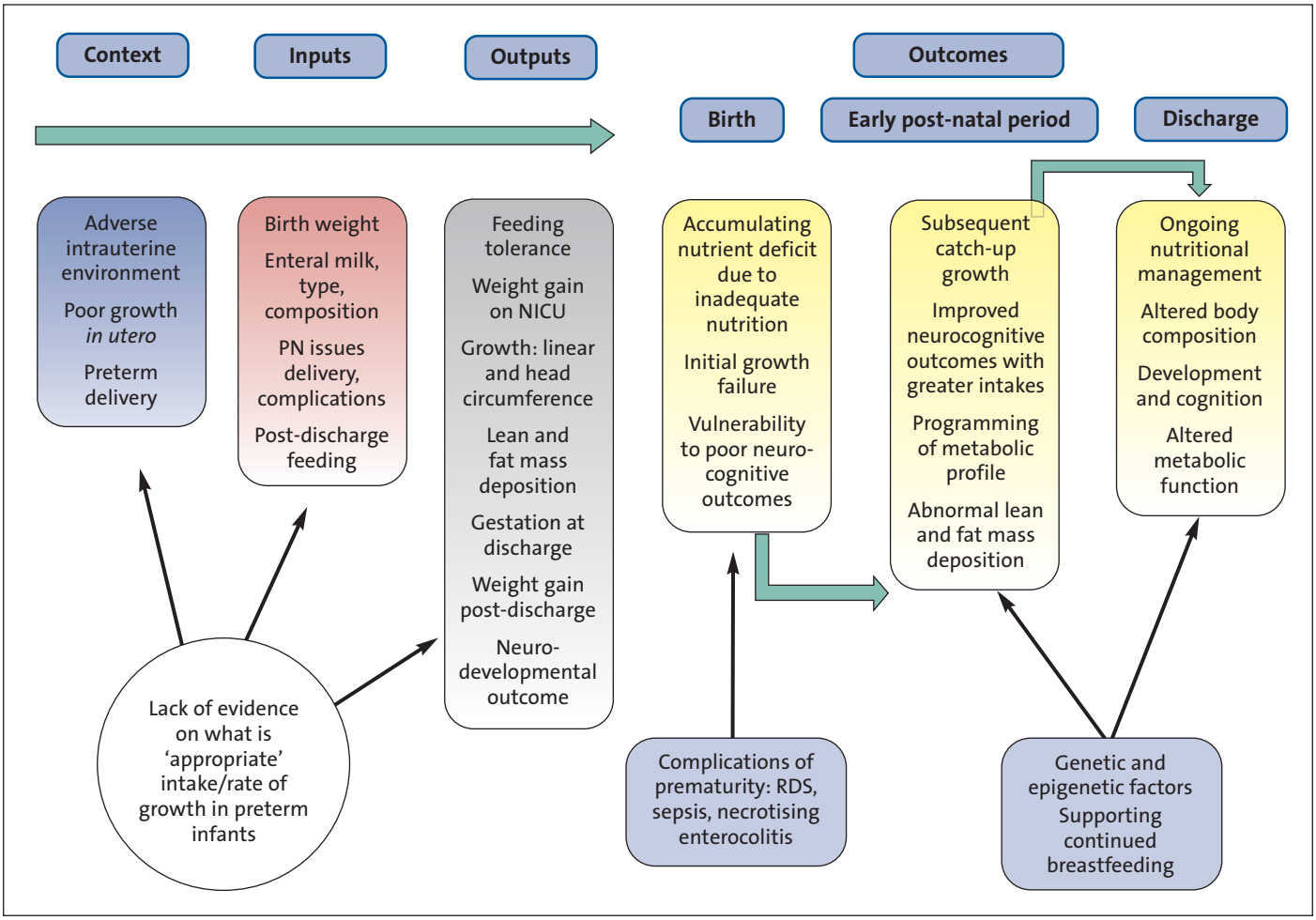

FIGURE 4 The logic model for catch-up growth in preterm infants. This summarises the context (prematurity), inputs (birth weight and postnatal nutrition), outputs (outcomes of care/measures of growth) and resulting short- and long-term outcomes. Key: PN = parenteral nutrition, RDS = respiratory distress syndrome, NICU = neonatal intensive care unit.

Disclosure statement

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