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REVIEW

Optimum feeding and growth in preterm neonates

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Approximately 10% of all babies worldwide are born preterm, and preterm birth is the leading cause of perinatal mortality in developed countries. Although preterm birth is associated with adverse short- and long-term health outcomes, it is not yet clear whether this relationship is causal. Rather, there is evidence that reduced foetal growth, preterm birth and the long-term health effects of both of these may all arise from a suboptimal intrauterine environment. Further, most infants born preterm also experience suboptimal postnatal growth, with potential adverse effects on long-term health and development. A number of interventions are used widely in the neonatal period to optimise postnatal growth and development. These commonly include supplementation with macronutrients and/or micronutrients, all of which have potential short-term risks and benefits for the preterm infant, whereas the long-term health consequences are largely unknown. Importantly, more rapid postnatal growth trajectory (and the interventions required to achieve this) may result in improved neurological outcomes at the expense of increased cardiovascular risk in later life.

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Introduction

It is estimated that 10% of all births are preterm, and this incidence is increasing worldwide.[1] Every year, over 1 million infants die because of complications associated with preterm birth, which is the leading cause of neonatal mortality worldwide and the second leading cause of death among children under 5 years of age.[1] Preterm babies are also frequently born small-for-gestational-age, and there is a large body of epidemiological evidence indicating that reduced size at birth is linked to increased risk of developing a number of diseases in later life. These include hypertension,[2] impaired glucose tolerance,[3] obesity[4,5] and coronary heart disease.[6,7]

Earlier studies focused on reduced size at birth in babies born at term, which was assumed to result from impaired foetal growth. However, more recent studies suggest that preterm birth, independent of foetal growth rate and even at late preterm gestations, is itself associated with increased blood pressure,[8] altered blood pressure regulation,[9] diabetes and insulin resistance,[10–14] as well as ischaemic heart disease and stroke[15] in later life. The adverse short- and long-term neurological and social outcomes of preterm birth are well known.[16,17] Nonetheless, it is becoming increasingly apparent that the adverse metabolic and neurodevelopmental outcomes following preterm birth not only affect those born at the extremes of viability but appear to be present as a graded response across preterm gestations, right up to and including late preterm births.[8,18]

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Both infants born preterm and those who experience intrauterine growth restriction (IUGR) are exposed to early environmental stress and suboptimal nutrition. This insult becomes apparent clinically during the later stages of pregnancy in IUGR infants, whereas for those born preterm this nutritional restriction occurs early in postnatal life, which is comparable to the third trimester of pregnancy.[19] However, preterm infants are also much more likely to experience poor growth *in utero*, and those infants born extremely preterm (24–32 weeks) appear to grow poorly as early as the first trimester of pregnancy.[20] As a result, the rate of IUGR is much greater among infants born preterm than those born at term,[21] and it has been estimated that 40% of preterm babies have also experienced IUGR.[22] The origins of a significant proportion of IUGR, such as that secondary to placental vascular disease, also lie in early pregnancy.

The causes of preterm birth are multi-factorial;[23] however, irrespective of the underlying causes, most infants born preterm also experience suboptimal postnatal growth. Further, although this suboptimal growth is often most profound in the immediate postnatal period,[24] it may also persist through childhood and adolescence. After the neonatal period, this suboptimal growth may be in part a result of alterations in the endocrine regulation of growth, which appears to be disrupted in preterm children and adolescents, so that growth is no longer associated with its normal hormone regulators.[19] However, a major contributor to postnatal faltering growth in infants born preterm is nutritional disruption due to inadequate nutrient intake.[25] It is common practice in neonatal units worldwide to increase intravenous nutrition incrementally in preterm infants over the 1st week of life and to introduce enteral feeds

cautiously. When compared with estimated placental nutrient transfer *in utero*,[25] there is an inevitable and substantial nutrient deficit, particularly for nitrogen, by the end of the 1st week.[26] This deficit occurs even if the latest recommended nutritional intakes are met, and contributes to early postnatal growth faltering. There are potentially serious consequences for the preterm infant, as postnatal malnutrition not only hinders somatic growth but may also adversely affect organ growth, structure and function.[22]

Poor early postnatal growth is likely to be associated with adverse neurodevelopmental outcomes,[24,27] but this relationship may be modifiable by other factors such as breastfeeding. In a recent large population study, infants born very preterm who were breastfed at the time of hospital discharge had significantly better neurodevelopmental outcomes than those who did not receive mothers' milk, despite an increased risk for poor early postnatal weight gain.[28] Thus, both early diet and early growth appear to be important mediators of later developmental outcomes.[28] However, it is important to appreciate that, in studies on breastfeeding, there are often confounding factors; in these studies, <20% of babies were breastfed at discharge, and maternal demographics were very different among breastfed and non-breastfed babies.

Cause and effect

Although preterm birth itself is associated with adverse short- and long-term health outcomes, it is not yet clear whether this relationship is causal. Rather, there is evidence that reduced foetal growth, preterm birth and the long-term health effects of both of these may all arise from a suboptimal intrauterine environment. In addition, there is some evidence that decreased foetal growth and shorter gestation length may also be linked to common antecedents, suggesting that further research into this area is warranted. In humans, for example, poor maternal nutrition before pregnancy or in the periconceptional period is associated with an increased risk for preterm birth.[23] Mothers who are underweight before pregnancy are also more likely to deliver preterm.[29,30] Twins are born both early and small,[31] outcomes that seem to have their origin in early pregnancy[32] and which appear to be linked.[33] Further, poor maternal nutrition is also associated with poor long-term health in the offspring.[34]

Animal studies have provided more conclusive evidence of the causal relationships involved. In sheep, maternal undernutrition around the time of conception led to preterm delivery in a proportion of animals.[35] Maternal undernutrition before conception also impaired the normal development of insulin resistance during pregnancy, which in turn was related to impaired foetal growth.[36] However, following periconceptional undernutrition, even the lambs born at term had evidence of disrupted regulation of early postnatal growth,[37] and in adulthood had altered body composition,[109] impaired glucose tolerance[38] and blunted adrenal response to corticotrophic stimulation.[39] These data suggest that nutritional factors before and around the time of conception, rather than preterm birth itself, may be the primary cause of subsequent adverse outcomes.

Interventions

At an equivalent gestational age, a preterm infant has a very different nutritional intake from that supplied by the placenta to a foetus. During the second and the beginning of the third trimester of pregnancy, the estimated placental transfer to the foetus is 3.6–4.8 g/kg.d of protein and 12–14 g/kg.d of glucose.[40] *In utero*, protein uptake by the foetus exceeds the amount needed for protein accretion, and the excess is oxidised to produce energy. The total foetal requirement for fatty acids at mid-gestation is ~1 g/kg.d, suggesting that oxidation of fatty acids for energy is relatively unimportant in foetal life.[40] In comparison, guidelines for intravenous nutrition in preterm infants recommend high intakes for both fat (3.0–4.0 g/kg.d) and carbohydrate (up to 18 g/kg.d), with a much lower protein content (1.5–4.0 g/kg.d) than the estimated placental transfer.[41,42] However, in clinical practice, these nutrient intakes are difficult to meet with current intravenous nutrition solutions and delivery systems. In reality, many preterm infants receive very low protein intakes in the first few days after birth,[43,44] resulting in large deficits in energy and protein.[45,46] Further, the amount and ratio of macronutrients given intravenously to preterm infants differ from the estimated *in utero* supply. These differences may promote the accretion of fat mass rather than lean body mass and may explain some of the observed differences in the body composition between preterm and term babies.[47–49]

Higher protein and energy intakes in preterm infants during the first few days after birth reduce growth faltering at discharge.[50–55] Other studies report favourable effects of earlier and/or higher total protein intake on the incidence of chronic lung disease,[56–58] although most studies found no differences in clinical outcomes.[50,59–61] Nonetheless, a nutritional approach that matches the estimated foetal macronutrient intakes has yet to be developed. Furthermore, protein intake is not the only determinant of growth, as an adequate balance of macronutrients and micronutrients is crucial for optimal growth and development in early postnatal life.[62]

Breast milk is widely recognised to be the best enteral feed, but it is inadequate to sustain postnatal growth of preterm babies at intrauterine growth rates. Importantly, the concentration of protein in expressed breast milk appears to be even lower than previously estimated.[63,64] Consequently, commercial breast milk fortifiers are commonly added to supplement the infant diet with additional quantities of protein and several other nutrients.[41,65] However, even with breast milk fortification, recommended enteral protein intakes are seldom achieved.[66–68] In addition, consensus recommendations for enteral protein intake were recently increased to 4.0–4.5 g/kg.d, resulting in the reformulation of several commercial breast milk fortifiers to increase the supplementary amount of added protein to

1.0–1.2 g per 100 ml breast milk and 2.5 g per 100 ml in some preterm formulae.[65]

There is growing evidence that manipulation of the macronutrient composition of milk leads to changes in weight gain and proportionality in the infant.[69,70] Systematic reviews report that both protein and multi-component breast milk fortification increase short-term growth parameters.[71,72] However, the level of protein fortification in the studies included in these reviews was lower than that supplied by newly available fortifiers, and the long-term effects of higher protein fortifiers and formulas are yet to be determined.

There is evidence that postnatal faltering growth is associated with adverse neurodevelopmental outcomes,[24,27] and improved growth over the first few months after birth has been shown to be associated with better outcomes at 18 months of age.[73] There is also evidence that nutrient-enriched formula provided to preterm infants after discharge may lead to improved later development.[73–75] A randomised trial of nearly 300 small-for-gestational-age infants born at term also showed significant gains in length and head circumference on an enriched formula.[76] However, this trial reported adverse developmental outcomes at 9 months of age, although these seem to have disappeared at 18 months.[77]

Further investigation is also required into the long-term effects of other dietary components in preterm neonates. For example, supplementation of breast milk with fat alone has little effect on postnatal growth.[78] However, additional long-chain polyunsaturated acids provided in breast milk via maternal supplementation are associated with improved problem-solving subscores (but not overall developmental scores) at the age of 6 months,[79] and in the Bayley mental development index at the age of 18 months in girls but not in boys.[80] A subgroup of children enrolled in this trial underwent an assessment of language skills, behaviour and temperament in early childhood (2–5 years of age); there were no significant differences between those who received docosahexaenoic acid supplementation and those who did not.[81] Data on possible later cardiovascular effects of these interventions are not yet available.

Similarly, some neonatal units routinely prescribe calcium supplementation for very preterm babies to facilitate appropriate bone growth. There are few good data to support this;[110] small trials have not found a benefit in bone mineral density by hospital discharge.[111] Supplementation of breast milk with a multi-nutrient fortifier for 12 weeks after discharge did result in higher calcium and phosphate intakes and increased skeletal growth but not bone density.[82] However, supplementation reduced milk intake in these infants, so that protein and energy intakes and body composition at the end of the intervention period were comparable between supplemented and unsupplemented infants. Nonetheless, it is conceivable that neonatal calcium intake may improve later cardiovascular outcomes, as maternal calcium supplementation during pregnancy has been shown to be associated with lowered blood pressure in the offspring.[83]

In lambs, ewe milk fortification (with a nutritional supplement analogous to breast milk fortifiers used clinically) for the first 2 weeks of life led to gestation- and sex-specific effects on early growth. For example, supplements altered growth in male but not female lambs, and resulted in increased weight-for-length (and by inference adiposity) at weaning in lambs born preterm but decreased adiposity in lambs born at term.[84] Some studies in humans have also shown differential effects in girls and boys following nutritional supplementation early in life.[85,86]

Importantly, nutritional supplementation given in the neonatal period may also affect later endocrine function. In sheep, for example, early nutritional supplementation altered glucose–insulin axis function in females, independent of growth.[84] Further, although supplementation reduced the insulin-secretory response to both glucose and arginine in female lambs born preterm, the response was increased in females born at term. In humans, diet in the neonatal period has also been shown to influence later glucose–insulin axis function in babies. When term infants of diabetic women were fed on either maternal milk or banked non-diabetic breast milk, those with the greatest exposure to 'diabetic' milk in the 1st (but not 2nd) week after birth had the greatest risk of glucose intolerance at 2 years,[87] irrespective of the total duration of breastfeeding.[88] The enteroinsular axis is known to be active at birth[89] and to be modified by both maturity[90] and diet.[91] It is therefore plausible that exposure to specific dietary components may modify pancreatic development in the newborn period. In addition, preterm infants have immature gastrointestinal tract function and experience delayed initiation of enteral feeding, as well as considerable variation in the type, composition and method of administration of milk feeds in the early neonatal period,[92] all of which may have significant implications for later metabolic function.

Apart from nutritional interventions, common neonatal morbidities and their treatment can also affect nutritional intake and growth. For example, in a prospective birth cohort from the United States, delivery by Caesarean section at term was associated with a twofold increased risk of obesity at 3 years of age.[93] In preterm infants, corticosteroids are used to treat ventilator-dependent chronic lung disease but can significantly impair growth in preterm babies.[94] Hyperglycaemia may affect over 50% of extremely low-birth-weight infants[95] and is associated with increased mortality and morbidity.[95,96] Hyperglycaemia in these babies is often managed by reducing glucose intake,[97] which may further impair growth. A recent clinical trial found that tight glycaemic control with insulin in hyperglycaemic preterm babies improved weight gain and mitigated the expected reduction in head circumference, suggesting a possible improvement in brain growth.[98] However, treatment reduced linear growth, suggesting an increase in fat mass. In addition, tight glycaemic control increased the risk for hypoglycaemia,[98] which is associated with poor neurodevelopmental outcomes in preterm babies.[99]

Potential risks and benefits

The majority of infants born preterm undergo accelerated growth after discharge, so that 85% reach the normal height range by 2 years of age.[100] Nonetheless, nutritional interventions are commonly introduced to further accelerate their growth, even though the long-term benefits and costs of such interventions are still unclear. In fact, a number of studies have suggested that accelerated growth in early childhood may actually be detrimental to health in the long-term.

For example, in a cohort of very preterm babies, those with growth rates in the highest tertile over the first 2 years of life had lower insulin sensitivity and higher blood pressure as young adults, compared with those in the lowest tertile.[14] Further, babies randomised to receive an enriched formula who exhibited accelerated neonatal growth had higher systolic blood pressure at 6–8 years of age than did babies fed a standard formula.[101] Accelerated neonatal growth for as little as 2 weeks after birth was associated with higher levels of a marker of insulin resistance in adolescence,[102] as well as with alterations in vasodilatation suggestive of impaired cardiovascular health.[103] The US Collaborative Perinatal Project studied nearly 56,000 pregnancies and showed that an increase in growth percentile during the first 7 years was associated with increased blood pressure.[104] A review of 21 studies identified that early accelerated growth (involving an increase of at least 0.67 weight SDS) was associated with a twofold to threefold increase in risk of overweight or obesity.[105,106] In addition, accelerated growth was associated with a greater likelihood of developing insulin resistance and subsequently the metabolic syndrome.[106] Thus, these findings have led some authors to question the wisdom of encouraging rapid weight gain in infants born preterm or IUGR.[104]

In contrast, other studies have observed beneficial effects of accelerated growth on neurodevelopmental outcomes. Preterm babies randomised to an enriched formula within 48 h of birth and fed this formula for an average of <6 weeks showed a one-third reduction in the risk for cerebral palsy in childhood.[77] Further, breastfed preterm babies supplemented with human milk fortifier for 6 weeks had accelerated growth with no adverse effects on neurodevelopment.[107] Observational studies have also reported that preterm babies who have higher growth rates in the neonatal period have higher neurodevelopmental scores in later life.[24,108]

The relationship between accelerated postnatal growth and long-term cognitive and metabolic health is difficult to tease out from the underlying causes of accelerated growth itself. It is also important to take into account the end result of accelerated growth for an individual, such as the relationship between final and starting growth (expressed as a *Z*-score or centile). Accelerated growth usually follows a period of faltering growth, whether this is before birth in IUGR babies, after birth in babies with postnatal growth faltering as for most very preterm babies, or both before and after birth as may occur in preterm babies born IUGR. There are currently no proven interventions for improving intrauterine growth in IUGR foetuses, suggesting that attention should be focussed on preventing the faltering postnatal growth that is so prevalent in babies born preterm.

Conclusions

Preterm birth is known to be associated with numerous short- and long-term adverse health outcomes. However, it is unclear whether these outcomes are a direct consequence of preterm birth itself or of associated factors, such as perturbed antenatal and/or postnatal growth and nutrition. There is evidence that both prenatal and postnatal nutritional restriction may contribute to adverse outcomes, and a number of interventions in the neonatal period have been shown to improve postnatal growth and development, at least in the short-term. Nonetheless, evidence for the long-term consequences of these interventions, particularly with respect to metabolic and cardiovascular health, is lacking, and most evidence on the long-term outcomes of neonatal nutrition and growth is epidemiological. High-quality prospective research in this area has lagged behind research in other aspects of neonatal care, and this deficit needs to be addressed. Future studies should attempt to dissect out the consequences of accelerated growth from its antecedents and whether the long-term risks and benefits of neonatal nutrition and growth, especially accelerated growth, may differ according to the outcome studied. This applies particularly to neurodevelopmental *v.* metabolic/cardiovascular outcomes, as targeting improvements in one aspect may involve a trade-off with respect to another.

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