Optimising Growth in Very Preterm Infants - Reviewing the evidence

Aneurin Young[a,b] (ORCID: 0000-0003-3549-3813, Twitter: @AneurinYoung), R Mark Beattie[c] (0000-0003-4721-0577, @RMBeattie50), Mark J Johnson[a,b] (0000-0003-1829-9912, @MarkJohnson800).

[a]Department of Neonatal Medicine, Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust, UK; [b]NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, UK; [c]Department of Paediatric Gastroenterology, Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust, UK;

Corresponding Author: Aneurin Young, Department of Neonatal Medicine, University Hospital Southampton NHS Foundation Trust, Coxford Road, Southampton, SO16 5YA, UK [a.young@soton.ac.uk] 02380777222

Word Count: 3143

This article has been accepted for publication in Archives of Disease in Childhood: Fetal and Neonatal Edition (2022) following peer review, and the Version of Record can be accessed online at: http://dx.doi.org/10.1136/archdischild-2021-322892 .

© NIHR Southampton Biomedical Research Centre (2022).

ABSTRACT

Infants born before 32 weeks postmenstrual age are at a high risk of growth failure. International guidelines have long recommended that they match the growth of an equivalent fetus, despite the challenges posed by ex-utero life and comorbidities of prematurity. Several groups have recently questioned the necessity or desirability of this target, shifting attention to aiming for growth which optimises important long-term outcomes. Specifically, recent research has identified the neurodevelopmental benefits of enhanced growth during the neonatal period, but work in term infant suggests that rapid growth may promote the metabolic syndrome in later life. In this context, defining a pattern of growth which optimises outcomes is complex, controversial and contested.

Even if an optimal pattern of growth can be defined, determining the nutritional requirements to achieve such growth is not straightforward, and investigations into the nutritional needs of the very preterm infant continue. Furthermore, each infant has individual nutritional needs and may encounter a number of barriers to achieving good nutrition.

This article offers a narrative review of recent evidence for the competing definitions of optimal growth in this cohort. It examines recent advances in the determination of macronutrient and micronutrient intake targets along with common barriers to achieving good nutrition and growth. Finally, key implications for clinical practice are set out and a recommendation for structured multidisciplinary management of nutrition and growth is illustrated.

INTRODUCTION

Preterm infants are vulnerable to poor growth. Transfer of nutrients from mother to infant during the third trimester of pregnancy is interrupted, and their postnatal nutritional intake is impaired by gut and metabolic immaturity. They are also prone to comorbidities which can also impair growth. Furthermore, defining what constitutes optimal growth (and conversely poor growth) has proven controversial.

In this narrative review, we aim to outline the importance of growth, to explore the definitions of optimal growth, to outline the evidence underpinning current nutritional best practice and to make practical recommendations for improving nutrition and growth.

Menon and colleagues have previously asked whether preterm nutrition is a trade-off between head and heart.[1] In other words, does enhanced nutrition improve neurodevelopmental outcomes at the expense of poorer cardiovascular health in later life? Over the last ten years, an increasing body of literature has shown that better weight gain in preterm infants is associated with better neurodevelopmental outcomes.[2-4] Belfort and co-workers have demonstrated that greater weight gain before term corrected age is associated with better neurodevelopmental outcomes.[3] They also identified that the most critical period for this effect is growth prior to and shortly after term equivalent age.[2]

At the same time, rapid weight gain in term infants is associated with development of the metabolic syndrome, a disease which is prevalent amongst ex-preterm infants. However, there are some data to suggest that rapid weight gain in early infancy for preterm infants is not associated with poorer metabolic outcomes, but that weight gain during subsequent phases of growth is a significant risk factor.[5] Recent results from the large observational EPICure study strongly suggest that the critical growth period for metabolic health is significantly later in childhood, between 2.5 and 6 years, whilst rapid growth prior to that period is not associated with an elevated risk.[6] Taken in conjunction, these neurodevelopmental and metabolic findings suggest that improved growth during early infancy, negating the impetus for later catch-up growth, may optimise neurodevelopmental outcomes without compromising metabolic health.

APPROACHES TO GROWTH STANDARDS

Guidelines set by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[7] and the American Academy of Pediatrics (AAP)[8] recommend that growth mimics that of the equivalent fetus in utero. However, preterm infants have consistently been found to grow more slowly than fetuses of equivalent postmenstrual age,[9] although this effect can be mediated by different nutritional approaches.[10] Additionally, preterm infants show marked differences in body composition compared to term-born infants,[11] therefore failing to achieve either the rate of

growth or the composition of weight gain called for by the two societies. Our recent meta-analysis identified the pattern of changing total body water percentage in newborns depending on gestation, with total body water falling from 90% to around 75% between 26 weeks gestation and term.[12]

Preterm infant growth standards can most easily be defined by taking measurements of newborn preterm infants. However, several groups have recently questioned this approach and the concept that ex utero growth should mimic the growth of a fetus in utero, leading to interest in redefining expected growth using other techniques.

The INTERGOWTH-21st Project

In 2014, the INTERGROWTH-21st Consortium monitored fetal growth and birthweight across an international cohort for whom comorbidity data were collected and pregnancies with confirmed fetal growth restriction were excluded. Birthweight data were used to form expected growth curves (Figure 1) but included only 382 subjects below 32 weeks gestation (of whom only 82 were below 28 weeks).[13] Data for length and head circumference were similarly limited.

Another arm of the INTERGROWTH project took an empirical approach, targeting growth which matches those of preterm infants who have suffered minimal postnatal complications. They recommend using standards derived from longitudinal data in low-risk preterms (Figure 1).[14]

The Southampton Preterm Cohort

We have previously shown that the growth of infants in Southampton can keep up with birthweight-derived growth standards.[10] These local Southampton data were used to generate a growth standard from a cohort of over 200 very preterm infants.[15] The resulting growth standard is based on repeated measurement of preterm infants in the context of fully described nutritional intakes (fig 1). A web application was also created to support the resultant charts (www.bit.ly/sotongrowth). Growth curves generally tracked close to UK-WHO growth standards generated from cross-sectional birthweight data.

Individualised Growth Targets

Landau-Crangle and co-workers have approached the question physiologically, arguing that adaptive early loss of body water will place the optimally-growing preterm infant on a lower centile followed by growth at a velocity such that the birth centile is matched only after the equivalent water loss of the term infant.[16] That group recommends individualised growth targets taking these factors into account (Figure 1).

Figure 1 illustrates the expected pattern of weight gain for an example infant born at 27 weeks postmenstrual age weighing 1kg. It compares the expected growth trajectory for a range of

approaches detailed above. Many of these curves match closely, with the individualised curve anticipating slower growth at first with subsequent convergence with the other tracks, and the INTERGROWTH longitudinal curve recommending more rapid growth throughout.

Table 1. Guideline recommendations for enteral and parenteral nutritional intakes for stable preterm infants along with the range nutritional intakes from some typical feeds (at 150ml/kg/day) and a commercially available parenteral nutrition product.

		ENTERAL FEEDING GUIDELINES		ENTERAL FEEDS					PARENTERAL FEEDING GUIDELINES		PARENTERAL FEEDING PRODUCT
		Koletzko et al.[17]	ESPGHAN[7]	Breastmilk (AAP[8])	Fortified Breastmilk	Preterm Formula	Preterm Follow-on Formula	Term Formula	ESPGHAN (2018)[18]	NICE[19]	Commercially Available Preterm PN
Nutrient	**Unit**	(per kg/day)	(per kg/day)	(per 150ml)	(per 150ml)	(per 150ml)	(per 150ml)	(per 150ml)	(per kg/day)	(per kg/day)	(per kg/day)
Energy	kcal	110-130	110-135	~100	120-130	120	110	100	90-120	75-120	116
Macronutrients											
Protein / Amino Acids	g	3.5-4.5	4-4.5 (<1kg body weight) 3.5-4 (>1kg body weight)	~1.4	3-4.5	4-4.5	3	2-2.2	2.5-3.5	3-4	3.8
Lipid	g	4.8-6.6	4.8-6.6	~5	5-6	5.5-6	5.5-6	5	3-4	3-4	3.2
Carbohydrate	g	11.6-13.2	11.6-13.2	~12	13-16	12-13	10.5-11.5	11-12	8-10	9-16	17
Micronutrients											
Sodium	mg	69-115	69-115	~20-40	70-90	80-100	40-50	30-50	46-115	Responsive*	165
	mmol	3-5	3-5	~1-2	3-4	3.5-4.5	1.8-2.4	1-2	2-5		2.8
Potassium	mg	78-195	66-132	~60-80	120-150	120-170	120-130	100-140	78-117	Responsive*	103
	mmol	2-5	1.7-3.4	1.5-2	2.5-3.5	3-4.5	3-3.5	2.5-3.5	2-3		2.6
Calcium	mg	120-200	120-140	~30-40	130-150	150-180	125	70	64-140	60-80	65
	mmol	3-5	3-3.5	0.7-1	3.5-4	4-4.5	3.1	1.7	1.6-3.5	1.5-2	1.6
Phosphorus	mg	60-140	60-90	~20	80-90	100-120	70-75	40-50	50-108	60	50
	mmol	2-4.5	2-3	0.6	2.5-3	3-4	2-2.5	1.3-1.6	1.6-3.5	2	1.6
Iron	mg	2-3	2-3	~0.05-0.14	0-3**	2-2.5	1.1-1.8	0.5-0.8	0	0	0
Zinc	mg	1.4-2.5	1.1-2	~0.15-0.5	1-2	1.5-2	1.3	0.8	0.4-0.5	NG	0.25
Vitamin A	µg RE	400-1100	400-1000	~50-90	400-600	500-550	100-150	90	227-455	NG	276
Vitamin D	IU	400-1000	800-1000	~0.05	250-300	180-200	100	90	80-400	NG	160
Vitamin E	mg α-TE	2.2-11	2.2-11	~0.5-1.2	5-7	5.5-7	1.3-3	1.7-2.1	2.8-3.5	NG	2.6
Vitamin K1	µg	4.4-28	4.4-28	~0.3-0.5	10-15	9-10	6-9	5-7	10	NG	80
Choline	mg	8-55	8-55	NG	3-3.5	30-40	35	33	NG	NG	NG
DHA	mg	55-60	12-30	NG	2-2.5	30-40	30	25	42	NG	NG

RE, retinol equivalents; α-TE, α-tocopherol equivalents; NG, no guidance given or not defined in product information

* Guidance recommends adjusting intake based on clinical sampling. ** Some fortifiers do not contain iron

ESTABLISHING NUTRITIONAL REQUIREMENTS

Notwithstanding difficulties in defining optimal growth, in practice it is necessary to set target nutrient intakes which may then be adjusted for individual infants based on their clinical status and growth trajectory. Table 1 presents several international guidelines for nutrient intake along with the nutritional provision of some typical feeds and parenteral nutrition products. Different methods have been used to define the recommended nutrient intakes. Historically, the factorial method aimed to estimate nutritional requirements by studying the changing composition of fetuses at different gestations.[20] More recently, experimental studies have examined the impact of changes in nutritional approach.

Experimental Approaches to Macronutrient Intakes

Several recent trials have randomized preterm infants to receive differing nutritional regimens. The NEON study assessed the impact of immediate or incremental increases in amino acid intakes and lipid emulsions during the first few days of life, with the control arm receiving up to 2.7g/kg/day amino acid by day 3 of life and the intervention arm receiving 3.6g/kg/day amino acid from day 1.[21] This study did not identify any differences in its primary outcomes of non-adipose mass and intrahepatocellular lipid. The group with higher early provision of amino acids had lower growth of head circumference 0.8 cm adjusted mean difference ($p=0.02$). The study was criticised for the minimal effect of allocation on actual macronutrient intake over the course of neonatal stay.[22]

The SCAMP Trial randomized infants to a control parenteral nutrition product or an intervention product which delivered more amino acid, lipid and glucose with a resultant higher energy provision throughout the period of parenteral nutrition.[23] Similarly to the NEON study, the control group were managed with PN containing amino acid at 2.8g/kg/day and the intervention group received amino acid at 3.8g/kg/day. However, the exposure to the allocated PN was for a significantly longer period, meaning that the total differences in nutrient intake were more pronounced. The group receiving more macronutrients had better head circumference growth to day 28 of life (the primary outcome, mean difference 5mm, $p<0.001$) and this persisted to 36 weeks corrected gestational age. Weight was unaffected as were all other tested clinical outcomes.

Similarly, a Norwegian group demonstrated an increased growth velocity to 36 weeks corrected GA in response to an enhanced supply of amino acid (comparing 3.2g/kg/day and 4g/kg/day amino acid intake), lipid and energy (17.4 vs 14.3 g/kg/day, $p<-0.001$).[24] A Dutch group randomized infants to a range of intakes of amino acids (2.4-3.6g/kg/day) and types of lipid, with one group (high amino acids and mixed lipid emulsion) demonstrating greater weight gain at two years corrected age but without any differences in neurodevelopment (the primary outcome).[25]

Each of these studies were performed before the most recent ESPGHAN parenteral nutrition guidelines. At the time of the studies, ESPGHAN recommended 1.5-4g/kg/day amino acid intake.[26] Therefore, they compared amino acid intakes within the recommended range at the time of the studies. It remains possible that substantially higher nutrient intakes than this may precipitate excess growth or detrimental derangement of body composition, although this possibility has not been tested in large studies to date. Taken together, these studies suggest that higher rates of nutritional intake lead to improved growth, although an impact on neurodevelopment remains unclear.

Experimental Approaches to Specific Micronutrients

A number of micronutrients have recently come under scrutiny, either for a possible general effect on growth or as targets for improving other specific clinical outcomes.

Trials of high doses of vitamin D supplementation have been shown to improve radiological markers of bone mineralization and to increase weight (13.6 vs 16.4g/day, $p<0.01$) and length gain (0.69 vs 0.79cm/week, $p=0.02$)[27]. Vitamin A supplementation has been shown to improve a marker of retinal function.[28]

Choline and docosahexaenoic acid are implicated in phosphatidylcholine metabolism and are found in high concentrations in fetal plasma, falling rapidly after preterm birth. A small trial has shown that supplementation with choline is practical and can restore plasma choline to near fetal concentrations although further work is needed to assess any potential impact on growth or neurodevelopment.[29]

A Cochrane review of LCPUFA supplementation in preterms found no proven effect.[30] Zinc has also risen to prominence in recent years, with a Cochrane review suggesting that enteral supplementation with zinc is likely to improve growth and reduce mortality.[31] This is particularly significant given that commonly available parenteral and enteral nutrition products typically deliver markedly insufficient amounts of zinc (Table 1), and zinc deficiency is common in preterm infants.[32]

BARRIERS TO ACHIEVING NUTRITIONAL TARGETS

Enteral Feed Tolerance

Feed intolerance is common and can be considered to be universal to some extent in the extremely preterm infant, most of whom require parenteral nutrition support at least in the first few weeks. However, parenteral nutrition presents significant risks, including central line associated bloodstream infection and cholestasis, as well as carrying significant financial cost. These problems have led to recent interest in accelerating enteral feed increments and restricting

the range of infants who receive parenteral nutrition. A recent systematic review highlighted the difficulties in defining feed intolerance, with inconsistent definitions frustrating attempts to formulate a consensus definition of feed intolerance in the preterm population.[33]

The SIFT trial concluded that increasing feeds at 30ml/kg/day (compared to 18ml/kg/day) reduced time to reaching full feeds.[34] The primary outcome of survival without moderate or severe neurodisability showed no difference between the groups. However, faster feeding was associated with an increased risk of moderate or severe motor impairment (adjusted effect 1.48, CI 1.02-2.14). An associated cost analysis identified that this excess of motor impairment meant that faster feeds are both clinically and economically undesirable.[35]

Observational data have demonstrated an association between early passage and clearance of meconium with improved enteral feed tolerance.[36] However, meta-analysis of studies aiming to improve enteral food tolerance by the prophylactic use of enemas or suppositories identified no effect of these interventions.[37]

The FEED1 trial is currently investigating whether giving full enteral feeds from the first day of life will decrease length of stay for infants born from 30^{+0} to 32^{+6} weeks gestation.[38]

Metabolic Tolerance

Metabolic disturbance is more common in the most preterm infants and in those with intrauterine growth restriction. The substantial energy needs of the preterm infant (Table 1) require the delivery of a significant load of carbohydrate, protein and lipid. However, these infants are prone to hyperglycaemia in the early neonatal period, which in turn have been associated with an increased risk of death, poor growth and most major morbidities associated with prematurity, although it is difficult to prove a causal link given the presence of likely confounding factors.[39] Technological advancements in continuous glucose monitoring have been shown to improve glycaemic control but the impact on outcomes remain uncertain.[40] Similarly, hypertrigyceridaemia is common at intravenous lipid delivery levels meeting nutritional requirements and is associated with poorer clinical outcomes.[41,42]

Parenteral Nutrition Limitations

Current formulations of parenteral nutrition often do not meet target or recommended nutrient requirements, especially for micronutrient minerals, particularly calcium and phosphate. In part, this is due to concerns about stability of these substances in solution and the possibility of precipitation. Studies continue in this area, especially as there is a pressing need to optimise calcium and phosphate delivery to prevent metabolic bone disease of prematurity.[43]

Sepsis and Inflammation

Preterm infants frequently experience episodes of inflammation, both from infections and from other causes, including surgical interventions. Infection is common, with around 10% of preterm infants experiencing late onset infection (Vermont Oxford Network VLBW cohort).[44] Acute inflammation profoundly alters the metabolic state of the preterm infant, driving catabolism, insulin resistance and suppression of growth factors such as IGF-1.[45] This is likely to lead to less effective nutrient metabolism with usual or increased nutrition in this context likely to drive hyperglycaemia and hypertriglyceridaemia without contributing to growth. This theoretical problem is reflected in well-established findings in critically ill adults and children, where early aggressive parenteral nutrition during acute illness is deleterious.[46,47]

Fluid Restriction

Newborn infants have a limited capacity for diuresis and so fluid intake is often limited during the first few days of life. In addition, fluid restriction may be part of medical management, for example in the presence of patent ductus arteriosus. Even once total fluid restriction is relaxed, there is often a period during which breastmilk replaces much more energy-dense parenteral nutrition. These multiple restrictions of fluid intake inevitably limit delivery of nutrition. These difficulties may be addressed by strategies including increasing the concentration of parenteral nutrition (as recommended by NICE)[48] and by earlier initiation of breastmilk fortification.

Nutritional Content of Breastmilk

Mother's own breastmilk provides substantial benefits to the preterm infant and is recommended as the ideal basis for enteral feeding.[7,8] Using breastmilk in preference to formula also significantly reduces the risk of necrotising enterocolitis. However, breastmilk alone cannot provide adequate nutritional intakes and hence multicomponent fortification has been widely adopted. A Cochrane review in 2004 recommended routine fortification as it improves short-term growth and identified no increase in adverse events related to its use, albeit with insufficient long-term follow-up data to reach a conclusion on neurodevelopmental outcomes.[49]

Breastmilk fortifier is typically formulated using extensively hydrolysed cow's milk protein. During the last decade, milk fortification products based on donated human milk have been developed. Initial studies establishing the use of the first of these products were troubled by design flaws and there is ongoing controversy surrounding its potential benefits and costs.[50] A recent systematic review and meta-analysis concluded that there is a suggestion of decreased risk of necrotising enterocolitis with human milk-based fortifier but that the overall quality of evidence is low and so its routine use cannot currently be recommended.[51]

Individualised Breastmilk Fortification

Maternal milk constitution and infant nutritional requirements are both highly variable. Therefore, attempts have been made to personalise breastmilk fortification to adjust breastmilk nutritional contents to prespecified values[52] or in response to infant blood urea level,[53] or both.[54] A study adjusting fortification in response to breastmilk analysis demonstrated an improvement in weight gain and a trend towards improved linear growth in the intervention arm.[52] Altering fortification in response to blood urea has shown promise in improving growth,[53] although there was significantly higher protein provision to the intervention group, meaning that it is difficult to know whether increased protein or personalisation per se was the important factor. A Cochrane review identified that targeted fortification improved weight, length and head growth during initial neonatal stay but that there was insufficient evidence for other outcomes.[55]

Donor Breastmilk

Milk banking has increased the availability of donated breastmilk throughout North America and Europe during the last decade. A recent Cochrane review addressed many questions relating to the relative safety and efficacy of fortified donor breastmilk compared to preterm formula.[56] Weight and length gain were better in the formula-fed group, with no difference in head growth or neurodevelopmental outcomes. Necrotising enterocolitis was more common in the formula fed group (risk ratio 1.87, 95%CI 1.23-2.85).

PRACTICAL MANAGEMENT OF NUTRITION AND GROWTH

Monitoring the growth of very preterm babies presents a number of challenges. Clinically unstable infants may be difficult to remove from their incubators to measure, although incubator scales can be used effectively.[57] Head circumference measurements may be difficult in the presence of respiratory support and length measurements may be difficult to perform accurately. In addition, fluid shifts may cause difficulty in interpreting weight gains and losses.

Monitoring the growth of preterm infants and tailoring their nutritional interventions is a complex task which requires the expertise of a multidisciplinary team, involving doctors, nurses, dietitians, pharmacists and other team members depending on the individual infant. There have been successful efforts to implement routine nutritional risk assessment, growth reviews and multidisciplinary shared decision-making based on comprehensive nutritional guidelines[58] with a resultant weight gain pattern which more closely follows birthweight-derived UK-WHO growth curves.[10,15] Figure 2 provides an outline of the factors to be considered during multidisciplinary review of growth and nutrition.

Implications for Practice

This evidence review highlights several practical interventions which have been shown to improve growth in the very preterm infant:

- Weight, length and head circumference should be routinely measured, at least weekly for length and more frequently for weight and head circumference
- Measurements should be plotted on a growth chart derived from a growth standard appropriate to the population in question. Further research is required to confirm whether individualised growth trajectories are preferable to standard birthweight-derived charts.
- There should be a standardised approach to the provision of enteral and parenteral nutrition, which is designed to meet published nutritional requirements (see table 1).
- Enteral or parenteral nutrition should be started as soon after birth as feasible
- Enteral feeding should be based on human breastmilk whenever possible.
- Breastmilk fortifier should be used to supplement human breastmilk so that it meets published nutritional requirements. Current data are insufficient to recommend human milk-based fortifier in preference to cows milk-based fortifier.
- Feeding increments of 18-30ml/kg/day seem reasonable, but the lower end of this range should be used for the most premature infants.
- Parenteral nutrition products should be formulated at concentrations which optimise nutritional intake, especially when total fluid intake is restricted.
- In the absence of strong evidence in neonatal populations, a temporary reduction in nutritional intake during acute inflammatory states should be considered in term infants based on evidence from children and adults. More data is needed to determine the best approach in preterm infants.
- There should be regular multidisciplinary monitoring of growth and planning of nutritional management to infants at risk of nutritional compromise.

CONCLUSION

Optimal growth is difficult to define and to deliver to very preterm infants. Whilst it is possible to set general targets for growth and nutritional intake, the requirements of any individual infant are defined by a set of complex and interacting factors. Future research is likely to focus on determining factors which can be used to tailor individualised approaches to nutrition, thereby optimising growth, avoiding morbidity and promoting health and neurodevelopment into childhood.

FIGURE LEGENDS

Figure 1.Examples of expected growth curves for a male infant born at 27 weeks weighing 1kg, generated by tracking a constant centile from the INTERGROWTH birthweight and postnatal growth standards,[14] the Fenton growth chart,[59] UK-WHO growth chart[60], growth chart generated from a Southampton cohort[15] and by calculating an individualised growth trajectory as per Landau-Crangle et al.[16] Figure created by the first author.

Figure 2. A multidisciplinary approach to growth assessment and decision-making. Figure created by the first author.

REQUIRED STATEMENTS

ACKNOWLEDGEMENTS: None

COMPETING INTERESTS: All authors have no conflicts of interest to disclose.

FUNDING SOURCE: The study was supported by the National Institute for Health Research Biomedical Research Centre Southampton, UK.

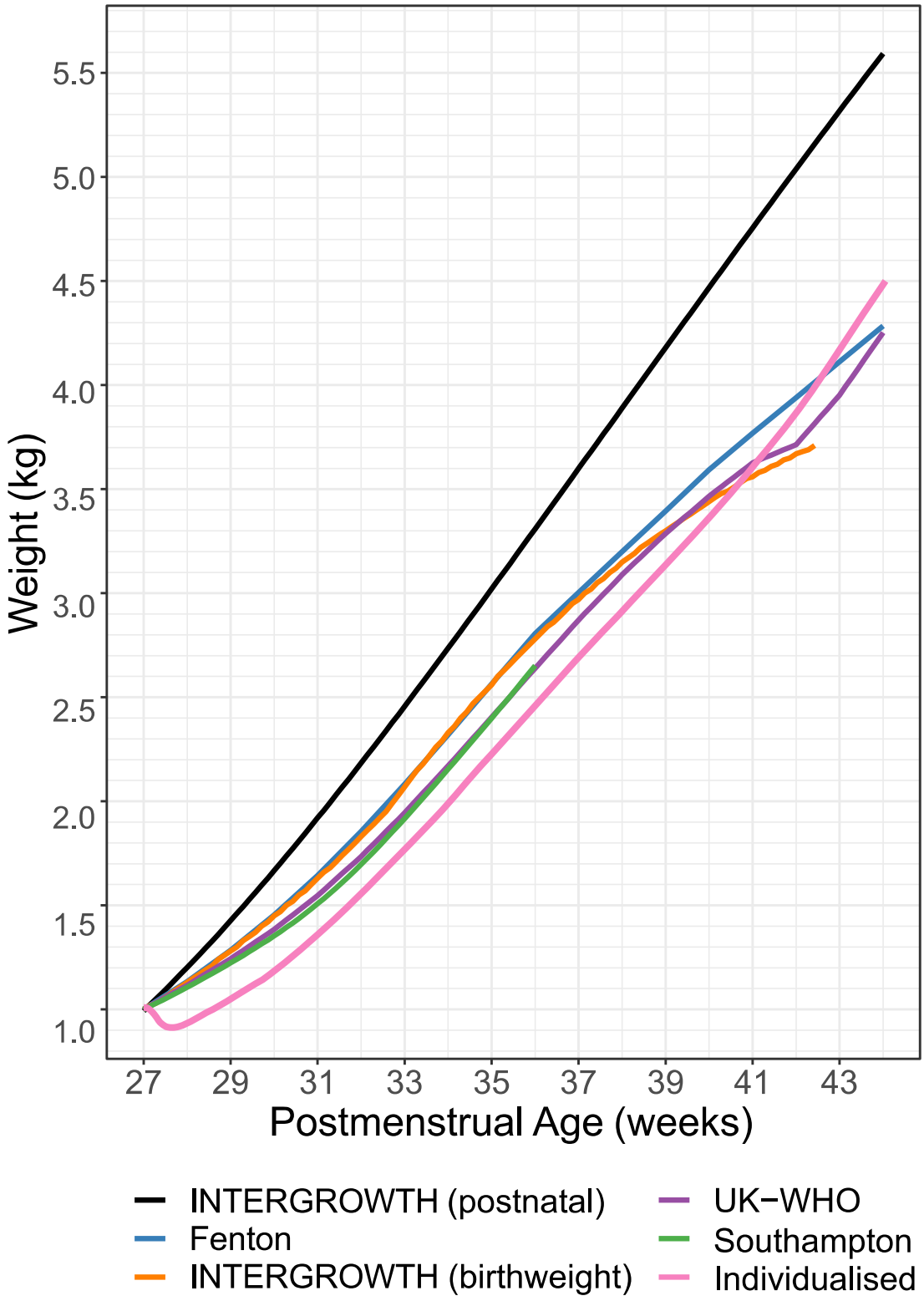
CONTRIBUTORSHIP: AY contributed to the conception, design and drafting of the work. RMB and MJJ contributed to the conception and design of the work, and to critical revision of the work for important intellectual content.

REFERENCES

1. Menon G, Davidson AL, Drake AJ, et al. Is preterm nutrition a trade-off between head and heart? *Arch Dis Child Fetal Neonatal Ed* 2019;104(3):F232-F34. doi: 10.1136/archdischild-2018-315672 [published Online First: 2018/10/14]
2. Leppanen M, Lapinleimu H, Lind A, et al. Antenatal and postnatal growth and 5-year cognitive outcome in very preterm infants. *Pediatrics* 2014;133(1):63-70. doi: 10.1542/peds.2013-1187 [published Online First: 2013/12/18]
3. Belfort MB, Rifas-Shiman SL, Sullivan T, et al. Infant growth before and after term: effects on neurodevelopment in preterm infants. *Pediatrics* 2011;128(4):e899-906. doi: 10.1542/peds.2011-0282 [published Online First: 2011/09/29]
4. Belfort MB, Martin CR, Smith VC, et al. Infant weight gain and school-age blood pressure and cognition in former preterm infants. *Pediatrics* 2010;125(6):e1419-26. doi: 10.1542/peds.2009-2746 [published Online First: 2010/05/19]
5. Embleton ND, Korada M, Wood CL, et al. Catch-up growth and metabolic outcomes in adolescents born preterm. *Arch Dis Child* 2016;101(11):1026-31. doi: 10.1136/archdischild-2015-310190 [published Online First: 2016/06/12]
6. Ni Y, Beckmann J, Hurst JR, et al. Size at birth, growth trajectory in early life, and cardiovascular and metabolic risks in early adulthood: EPICure study. *Arch Dis Child Fetal Neonatal Ed* 2021;106(2):149-55. doi: 10.1136/archdischild-2020-319328 [published Online First: 2020/08/17]
7. Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2010;50(1):85-91. doi: 10.1097/MPG.0b013e3181adaee0 [published Online First: 2009/11/03]
8. American Academy of Pediatrics Committee on Nutrition. Nutritional Needs of the Preterm Infant. In: Kleinman RE, Greer FR, eds. Pediatric Nutrition. 8th edition. ed. Itasca, IL: American Academy of Pediatrics, 2019.
9. Cole TJ, Statnikov Y, Santhakumaran S, et al. Birth weight and longitudinal growth in infants born below 32 weeks' gestation: a UK population study. *Arch Dis Child Fetal Neonatal Ed* 2014;99(1):F34-40. doi: 10.1136/archdischild-2012-303536 [published Online First: 2013/08/13]
10. Andrews ET, Ashton JJ, Pearson F, et al. Early postnatal growth failure in preterm infants is not inevitable. *Arch Dis Child Fetal Neonatal Ed* 2019;104(3):F235-F41. doi: 10.1136/archdischild-2018-315082 [published Online First: 2018/08/24]
11. Johnson MJ, Wootton SA, Leaf AA, et al. Preterm birth and body composition at term equivalent age: a systematic review and meta-analysis. *Pediatrics* 2012;130(3):e640-9. doi: 10.1542/peds.2011-3379 [published Online First: 2012/08/15]
12. Young A, Brown LK, Ennis S, et al. Total body water in full-term and preterm newborns: systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2021 doi: 10.1136/archdischild-2020-321112 [published Online First: 2021/04/02]
13. Villar J, Giuliani F, Fenton TR, et al. INTERGROWTH-21st very preterm size at birth reference charts. *Lancet* 2016;387(10021):844-5. doi: 10.1016/S0140-6736(16)00384-6 [published Online First: 2016/02/24]
14. Villar J, Giuliani F, Bhutta ZA, et al. Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21st Project. *Lancet Global Health* 2015;3(11):E681-E91. doi: Doi 10.1016/S2214-109x(15)00163-1
15. Young A, Andrews ET, Ashton JJ, et al. Generating longitudinal growth charts from preterm infants fed to current recommendations. *Arch Dis Child Fetal Neonatal Ed* 2020 doi: 10.1136/archdischild-2019-318404 [published Online First: 2020/05/27]
16. Landau-Crangle E, Rochow N, Fenton TR, et al. Individualized Postnatal Growth Trajectories for Preterm Infants. *JPEN J Parenter Enteral Nutr* 2018;42(6):1084-92. doi: 10.1002/jpen.1138 [published Online First: 2018/02/09]
17. Koletzko B, Poindexter B, Uauy R. Recommended nutrient intake levels for stable, fully enterally fed very low birth weight infants. *World Rev Nutr Diet* 2014;110:297-9. doi: 10.1159/000360195 [published Online First: 2014/04/23]
18.
20. Ziegler EE, O'Donnell AM, Nelson SE, et al. Body composition of the reference fetus. *Growth* 1976;40(4):329-41. [published Online First: 1976/12/01]
21. Uthaya S, Liu X, Babalis D, et al. Nutritional Evaluation and Optimisation in Neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid

composition in preterm parenteral nutrition. *Am J Clin Nutr* 2016;103(6):1443-52. doi: 10.3945/ajcn.115.125138 [published Online First: 2016/04/22]
22. Embleton ND, Van Den Akker CH. Early parenteral amino acid intakes in preterm babies: does NEON light the way? *Arch Dis Child Fetal Neonatal Ed* 2018;103(2):F92-F94. doi: 10.1136/archdischild-2017-313406 [published Online First: 2017/10/04]
23. Morgan C, McGowan P, Herwitker S, et al. Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study. *Pediatrics* 2014;133(1):e120-8. doi: 10.1542/peds.2013-2207 [published Online First: 2014/01/01]
24. Strommen K, Haag A, Moltu SJ, et al. Enhanced nutrient supply to very low birth weight infants is associated with higher blood amino acid concentrations and improved growth. *Clin Nutr ESPEN* 2017;18:16-22. doi: 10.1016/j.clnesp.2017.01.003 [published Online First: 2017/11/15]
25. Roelants JA, Vlaardingerbroek H, van den Akker CHP, et al. Two-Year Follow-up of a Randomized Controlled Nutrition Intervention Trial in Very Low-Birth-Weight Infants. *JPEN J Parenter Enteral Nutr* 2018;42(1):122-31. doi: 10.1177/0148607116678196 [published Online First: 2016/11/23]
26. Koletzko B, Goulet O, Hunt J, et al. 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 2005;41 Suppl 2:S1-87. doi: 10.1097/01.mpg.0000181841.07090.f4
27. Mathur NB, Saini A, Mishra TK. Assessment of Adequacy of Supplementation of Vitamin D in Very Low Birth Weight Preterm Neonates: A Randomized Controlled Trial. *J Trop Pediatr* 2016;62(6):429-35. doi: 10.1093/tropej/fmv110 [published Online First: 2016/06/22]
28. Mactier H, McCulloch DL, Hamilton R, et al. Vitamin A supplementation improves retinal function in infants at risk of retinopathy of prematurity. *J Pediatr* 2012;160(6):954-9 e1. doi: 10.1016/j.jpeds.2011.12.013 [published Online First: 2012/01/31]
29. Bernhard W, Bockmann K, Maas C, et al. Combined choline and DHA supplementation: a randomized controlled trial. *Eur J Nutr* 2020;59(2):729-39. doi: 10.1007/s00394-019-01940-7 [published Online First: 2019/03/13]
30. Moon K, Rao SC, Schulzke SM, et al. Longchain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database Syst Rev* 2016;12:CD000375. doi: 10.1002/14651858.CD000375.pub5 [published Online First: 2016/12/21]
31. Staub E, Evers K, Askie LM. Enteral zinc supplementation for prevention of morbidity and mortality in preterm neonates. *Cochrane Database Syst Rev* 2021;3:CD012797. doi: 10.1002/14651858.CD012797.pub2 [published Online First: 2021/03/13]
32. Vazquez-Gomis R, Bosch-Gimenez V, Juste-Ruiz M, et al. Zinc concentration in preterm newborns at term age, a prospective observational study. *BMJ Paediatr Open* 2019;3(1):e000527. doi: 10.1136/bmjpo-2019-000527 [published Online First: 2019/10/28]
33. Weeks CL, Marino LV, Johnson MJ. A systematic review of the definitions and prevalence of feeding intolerance in preterm infants. *Clin Nutr* 2021;40(11):5576-86. doi: 10.1016/j.clnu.2021.09.010 [published Online First: 20210917]
34. Dorling J, Abbott J, Berrington J, et al. Controlled Trial of Two Incremental Milk-Feeding Rates in Preterm Infants. *N Engl J Med* 2019;381(15):1434-43. doi: 10.1056/NEJMoa1816654 [published Online First: 2019/10/10]
35. Tahir W, Monahan M, Dorling J, et al. Economic evaluation alongside the Speed of Increasing milk Feeds Trial (SIFT). *Arch Dis Child Fetal Neonatal Ed* 2020;105(6):587-92. doi: 10.1136/archdischild-2019-318346 [published Online First: 2020/04/04]
36. Mihatsch WA, Franz AR, Lindner W, et al. Meconium passage in extremely low birthweight infants and its relation to very early enteral nutrition. *Acta Paediatr* 2001;90(4):409-11.
37. Deshmukh M, Balasubramanian H, Patole S. Meconium Evacuation for Facilitating Feed Tolerance in Preterm Neonates: A Systematic Review and Meta-Analysis. *Neonatology* 2016;110(1):55-65. doi: 10.1159/000444075 [published Online First: 20160407]
38. Unit NCT. Fluids exclusively enteral from day one in premature infants: Nottingham Clinical Trials Unit, 2019.
39. van der Lugt NM, Smits-Wintjens VE, van Zwieten PH, et al. Short and long term outcome of neonatal hyperglycemia in very preterm infants: a retrospective follow-up study. *BMC Pediatr* 2010;10:52. doi: 10.1186/1471-2431-10-52 [published Online First: 2010/07/22]
40. Beardsall K, Thomson L, Guy C, et al. Real-time continuous glucose monitoring in preterm infants (REACT): an international, open-label, randomised controlled trial. *Lancet Child Adolesc Health* 2021 doi: 10.1016/S2352-4642(20)30367-9 [published Online First: 2021/02/13]

41. Giretti I, D'Ascenzo R, Correani A, et al. Hypertriglyceridemia and lipid tolerance in preterm infants with a birth weight of less than 1250 g on routine parenteral nutrition. *Clin Nutr* 2021 doi: 10.1016/j.clnu.2020.12.039 [published Online First: 2021/02/03]
42. Alburaki W, Yusuf K, Dobry J, et al. High Early Parenteral Lipid in Very Preterm Infants: A Randomized-Controlled Trial. *J Pediatr* 2021;228:16-23 e1. doi: 10.1016/j.jpeds.2020.08.024 [published Online First: 2020/08/18]
43. Wang HJ, Hsieh YT, Liu LY, et al. Use of sodium glycerophosphate in neonatal parenteral nutrition solutions to increase calcium and phosphate compatibility for preterm infants. *Pediatr Neonatol* 2020;61(3):331-37. doi: 10.1016/j.pedneo.2020.02.004 [published Online First: 2020/03/23]
44. Vermont Oxford Network. Vermont Oxford Network Annual Report 2019. Burlington, VT, USA, 2019:5.
45. Ramel SE, Brown LD, Georgieff MK. The Impact of Neonatal Illness on Nutritional Requirements-One Size Does Not Fit All. *Curr Pediatr Rep* 2014;2(4):248-54. doi: 10.1007/s40124-014-0059-3 [published Online First: 2015/02/28]
46. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011;365(6):506-17. doi: 10.1056/NEJMoa1102662 [published Online First: 2011/07/01]
47. Fivez T, Kerklaan D, Mesotten D, et al. Early versus Late Parenteral Nutrition in Critically Ill Children. *N Engl J Med* 2016;374(12):1111-22. doi: 10.1056/NEJMoa1514762 [published Online First: 2016/03/16]
48. Excellence NIfHaC. Neonatal parenteral nutrition. London, UK, 2020.
49. Kuschel CA, Harding JE. Multicomponent fortified human milk for promoting growth in preterm infants. *Cochrane Database Syst Rev* 2004(1):CD000343. doi: 10.1002/14651858.CD000343.pub2 [published Online First: 2004/02/20]
50. Embleton ND, King C, Jarvis C, et al. Effectiveness of human milk-based fortifiers for preventing necrotizing enterocolitis in preterm infants: case not proven. *Breastfeed Med* 2013;8(4):421. doi: 10.1089/bfm.2013.0049 [published Online First: 2013/06/12]
51. Grace E, Hilditch C, Gomersall J, et al. Safety and efficacy of human milk-based fortifier in enterally fed preterm and/or low birthweight infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2021;106(2):137-42. doi: 10.1136/archdischild-2020-319406 [published Online First: 2020/09/19]
52. Rochow N, Fusch G, Ali A, et al. Individualized target fortification of breast milk with protein, carbohydrates, and fat for preterm infants: A double-blind randomized controlled trial. *Clin Nutr* 2021;40(1):54-63. doi: 10.1016/j.clnu.2020.04.031 [published Online First: 20200506]
53. Arslanoglu S, Moro GE, Ziegler EE. Adjustable fortification of human milk fed to preterm infants: does it make a difference? *J Perinatol* 2006;26(10):614-21. doi: 10.1038/sj.jp.7211571 [published Online First: 2006/08/04]
54. Brion LP, Rosenfeld CR, Heyne R, et al. Optimizing individual nutrition in preterm very low birth weight infants: double-blinded randomized controlled trial. *J Perinatol* 2020;40(4):655-65. doi: 10.1038/s41372-020-0609-1 [published Online First: 2020/02/20]
55. Fabrizio V, Trzaski JM, Brownell EA, et al. Individualized versus standard diet fortification for growth and development in preterm infants receiving human milk. *Cochrane Database Syst Rev* 2020;11:CD013465. doi: 10.1002/14651858.CD013465.pub2 [published Online First: 2020/11/24]
56. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2019(7) doi: 10.1002/14651858.CD002971.pub5
57. El-Kafrawy U, Taylor RJ. Optimizing care of ventilated infants by improving weighing accuracy on incubator scales. *J Neonatal Perinatal Med* 2016;9(4):377-83. doi: 10.3233/NPM-161623 [published Online First: 2016/12/24]
58. Johnson MJ, Leaf AA, Pearson F, et al. Successfully implementing and embedding guidelines to improve the nutrition and growth of preterm infants in neonatal intensive care: a prospective interventional study. *BMJ Open* 2017;7(12):e017727. doi: 10.1136/bmjopen-2017-017727 [published Online First: 2017/12/09]
59. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2013;13:59. doi: 10.1186/1471-2431-13-59 [published Online First: 2013/04/23]
60. RCPCH. UK-WHO growth charts - neonatal and infant close monitoring (NICM) London, UK: Royal College of Paediatrics and Child Health; 2019 [Available from: .


5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Weight (kg)
27
29
31
33
35
37
39
41
43
Postmenstrual Age (weeks)
INTERGROWTH (postnatal)
Fenton
INTERGROWTH (birthweight)
UK−WHO
Southampton
Individualised

PRETERM NUTRITION MDT REVIEW

Dietitian, Neonatologist, Nurse, Pharmacist, Surgical Team

Describe Baby
- Gestation
- Age
- Growth restriction

Review Clinical Status
- Diagnoses
- Illness severity
  - Sepsis / Inflammation
  - Necrotising enterocolitis
- GI / Surgical Concerns
- Vascular access
- Medications
  - Steroids
  - Diuretics
- Fluid status
- Fluid restriction

Assess Growth
- Weight
- Length
- Head circumference
- Proportionality of growth
- Response to previous nutritional interventions

Calculate Intake
- Enteral
  - Type
  - Volume
  - Tolerance
- Parenteral
  - Type
  - Volume
- Nutrient intakes
  - Energy
  - Protein
  - Protein:Energy ratio
  - Carbohydrate
  - Fat
  - Micronutrients

Review Results
- Metabolic bone disease
- Glucose and lipid tolerance
- Electrolytes
- Micronutrients (vitamins, zinc etc.)

Set Targets
- Growth
  - Weight
  - Length
  - Head circumference
- Nutrient intakes
- Progression to enteral autonomy
- Resolution of abnormal results

Make a Plan
- Intake changes
  - Parenteral nutrition
    - Rate
    - Constitution
    - Standardised or bespoke
  - Enteral feeds
    - Volume
      - Incremental increases
    - Breastmilk
      - Maternal
      - Donor
      - Fortification
    - Formula type
  - Supplementation
    - Multivitamins
    - Iron
    - Electrolytes
    - Specific
      - Cholecalciferol / Alfacalcidol
      - Zinc
- Rechecking results
- Reviewing growth response
- Communicate
  - Medical team
  - Nursing team
  - Parents