Customizing Proteins, Fats and Carbs:
A Balancing Act in the NICU

Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS
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Learning Objectives

- Describe the unique nutritional needs of preterm infants
- Relate the protein needs of preterm infants with growth and development
- Identify preterm infants whose nutritional needs are changing

Nutrition in the NICU

Introduction

Nutrition Among Preterm Infants Is Frequently Suboptimal

- Many preterm infants are not receiving optimal amounts and types of nutrition, leading to growth faltering
- Despite the availability of more optimally designed early feeding guidelines, NICUs frequently do not follow evidence-based protocols
- Validated tools to assess growth are not used consistently

As a result, growth faltering among preterm infants is common and carries serious later life adverse consequences for body composition, neurodevelopment, metabolism, and growth.

NICU, neonatal intensive care unit.

Hay WW Jr. *Curr Pediatr Rep*. 2013;1(4):10.1007/s40124-013-0026-4.

Nutrition Among Preterm Infants Is Frequently Suboptimal Because Nutritional Support for Preterm Infants Is Associated With Unique Challenges

- Very rapid rates of growth and development require unique nutritional needs for energy, protein, minerals, and vitamins
- High metabolic demands, particularly for the brain and the heart, as well as for growth
- Minimal nutrient stores due to most nutrient accretion occurring in final weeks of gestation
- Limited ability to receive full enteral nutrition in early postnatal days

1. Hay WW, Jr. *Pediatr Gastroenterol Hepatol Nutr*. 2018;21(4):234-247.
2. Ziegler EE. *Ann Nutr Metab*. 2011;58 Suppl 1:8-18.

Goals of Preterm Nutrition

1. Achieve growth rates comparable with the normally growing healthy human fetus (eg, growth parameters follow the Fenton or Olsen growth curves)
2. Prevent extrauterine growth faltering

   Note: extrauterine growth faltering—not growing at normal fetal rates—is distinct from extrauterine growth restriction (EUGR) which is defined as weight less than an arbitrary percentile (eg, <10th percentile) at a later gestational age (eg, 36 weeks PMA). Not all small preterm (or term) infants are abnormal or experience growth faltering.

3. Optimize neurodevelopmental and other long-term outcomes

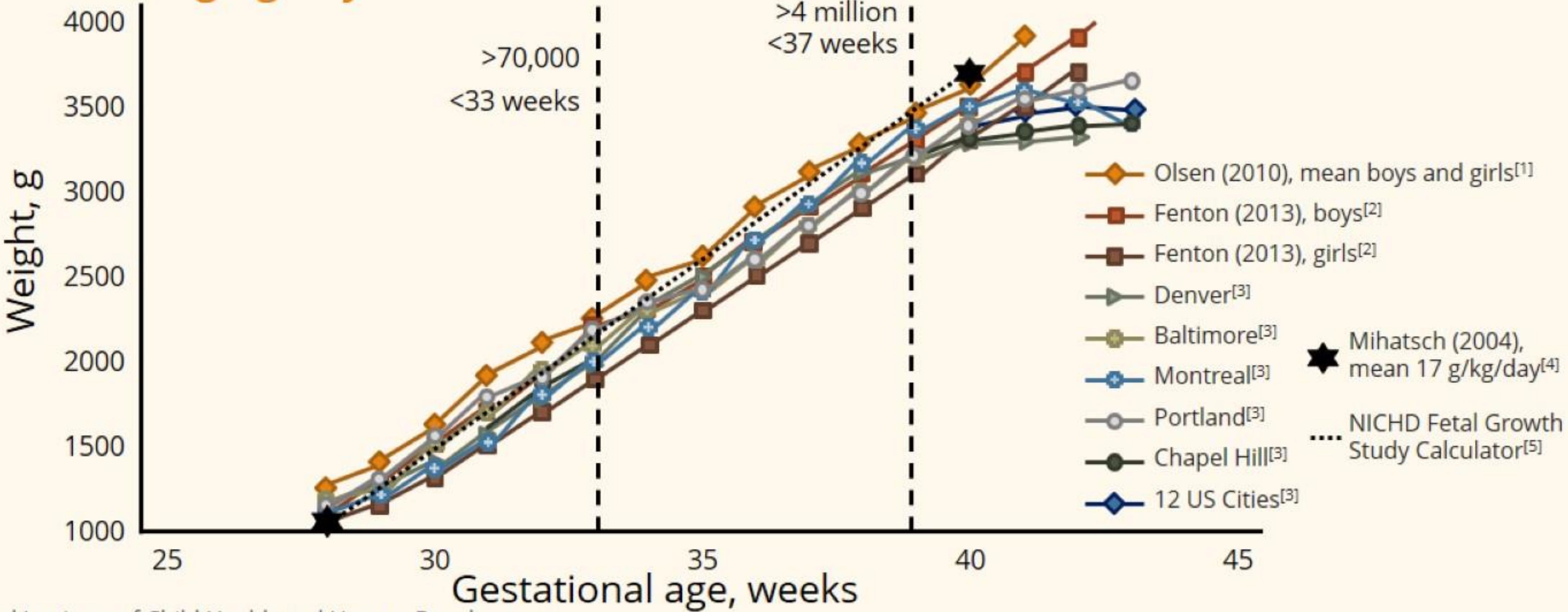
The **American Academy of Pediatrics** recommends that parenteral and enteral nutrition should "provide nutrients **to approximate the rate of growth and composition of weight gain for a normal fetus** of the same postmenstrual age and to maintain normal concentrations of blood and tissue nutrients."

PMA, postmenstrual age.

Hay WW, Jr. *Pediatr Gastroenterol Hepatol Nutr*. 2018;21(4):234-247.

What Is Normal Fetal Growth?

Growth references for preterm infants have been controversial, but among many different fetal growth references, **birth weight by gestational age is relatively constant from ~26 to 37 weeks** at **~15 to 20 g/kg/day**.

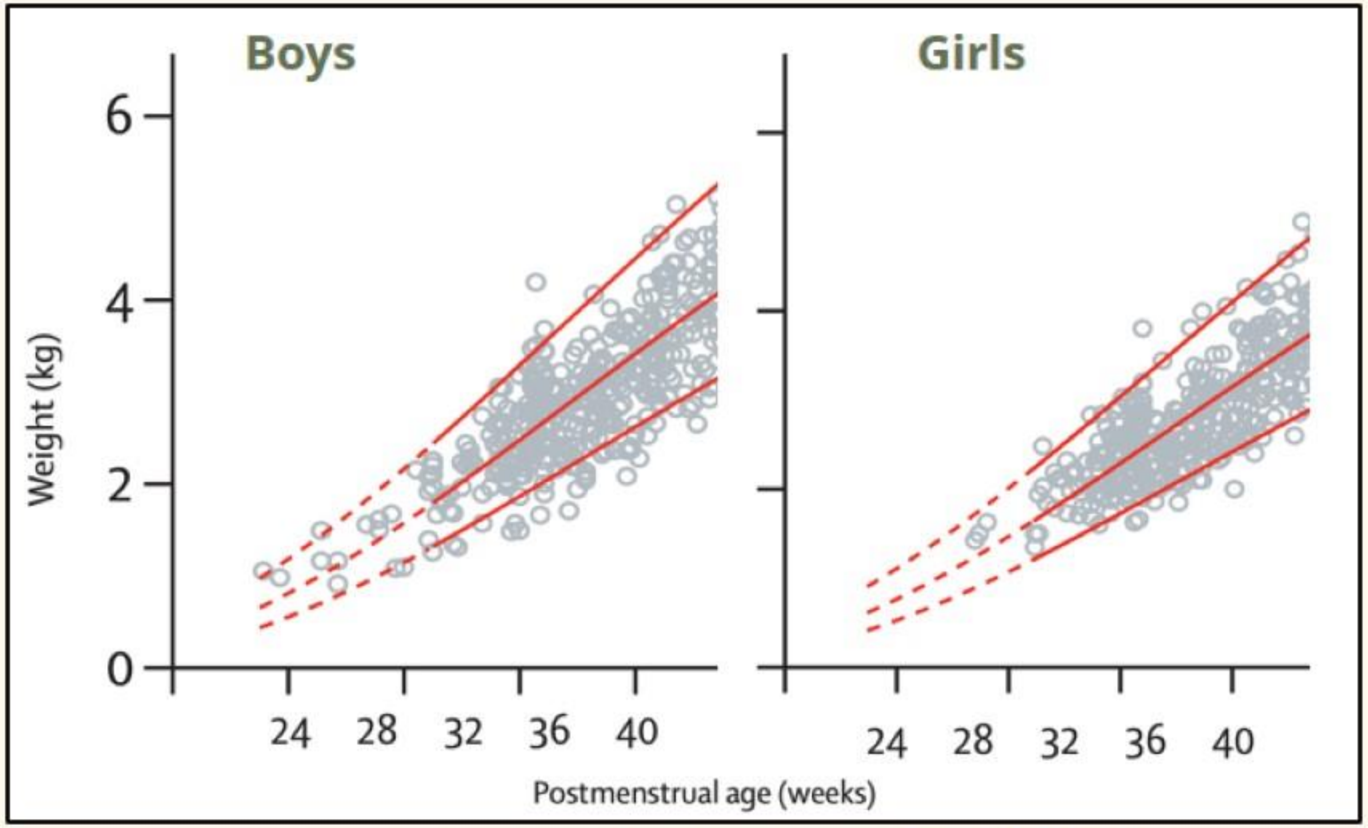


NICHD, National Institute of Child Health and Human Development.

1. Olsen IE, et al. *Pediatrics.* 2010;125(2):e214-e224.
2. Fenton TR, Kim JH. *BMC Pediatr.* 2013;13:59.
3. Naeye RL, Dixon JB. *Pediatr Res.* 1978;12(10):987-991.
4. NIH NICHD. March 3, 2020. Accessed October 7, 2020. https://www.nichd.nih.gov/fetalgrowthcalculator.

INTERGROWTH-21st Project Preterm Growth Charts

Few data: only 201 infants <37 weeks; only 28 infants <33 weeks; only 12 (9 boys and 3 girls) <32 weeks; no girls <30 weeks; and **not normally distributed**.



Fetal curves are projected from growth data of infants after birth

Pooled international populations, with more small infants from shorter mothers.

INTERGROWTH-21st Project Preterm Growth Charts

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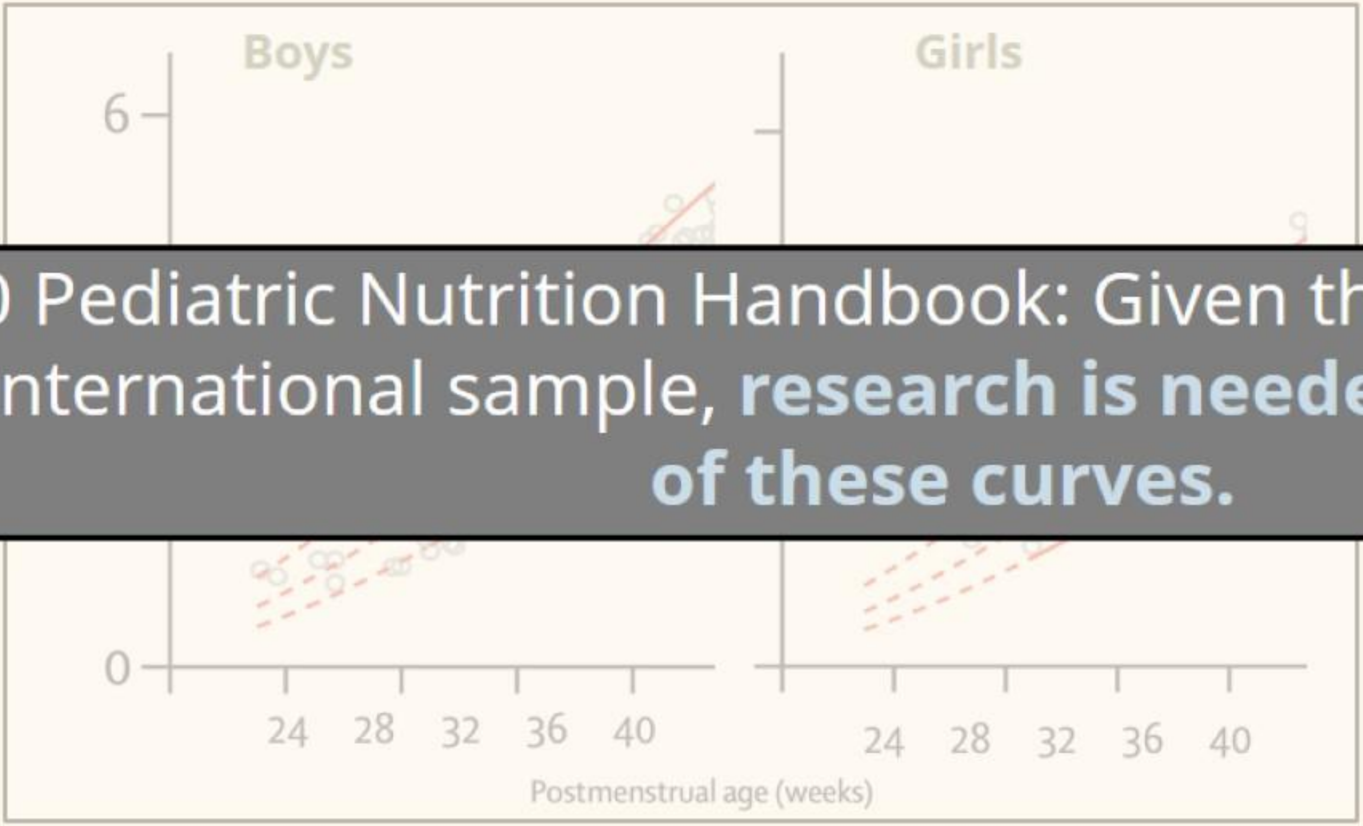


Fetal curves are projected from growth data of infants after birth

small infants from shorter mothers.

AAP 2020 Pediatric Nutrition Handbook: Given the small sample size and pooled international sample, **research is needed to evaluate the use of these curves.**

a. Image reproduced from Villar J et al. *Lancet Glob Health*. 2015;3(11):e681-e691. CC BY-NC-ND 4.0.

1. Villar J et al. Lancet Glob Health. 2015;3(11):e681-e691.
2. Kleinman RE, Greer FR. *Pediatric Nutrition, 8th ed*. November 15, 2019; American Academy of Pediatrics.

Growth Faltering by Fetal References, But NOT by INTERGROWTH-21st Is Associated With Worse Neurodevelopmental Outcomes in a North American Population

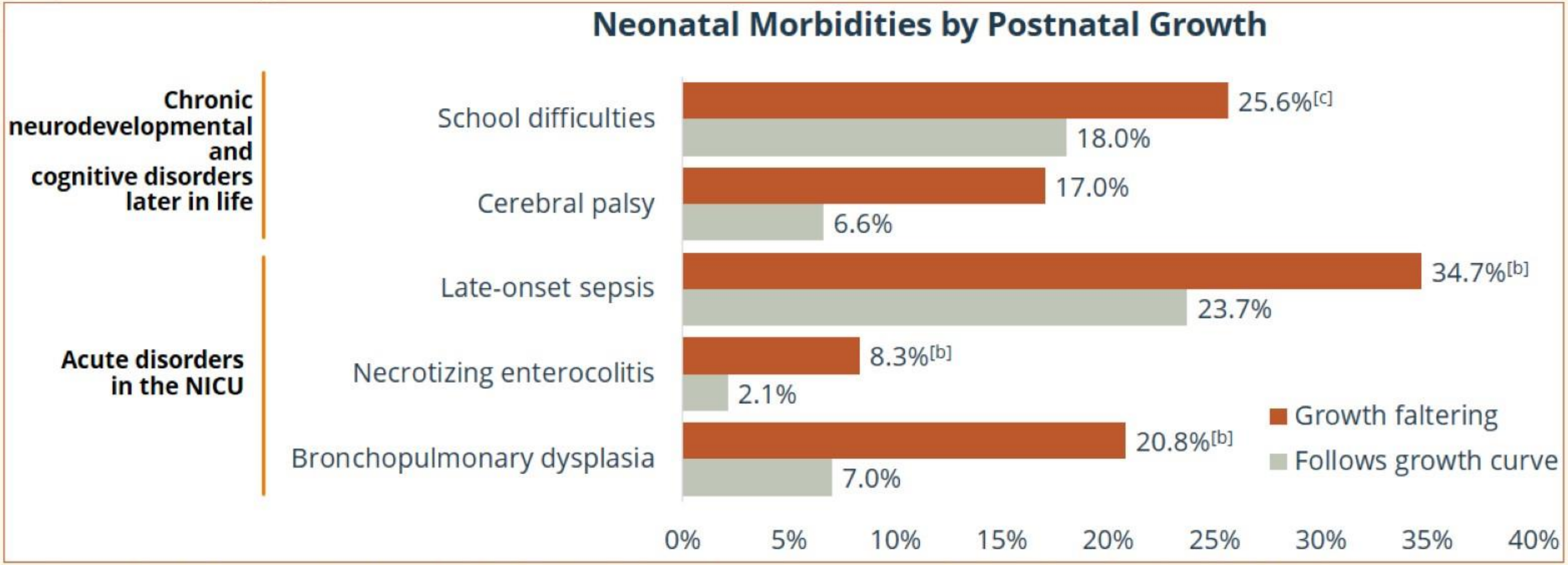
- Association of slower weight gain with Mental Developmental Index score <85 at 18 months:
  - Slower weight gain by Fenton reference: aOR, 1.6[a]; 95% CI, 1.1–2.4
  - Slower weight gain by INTERGROWTH-21st: aOR, 1.0; 95% CI, 0.6–1.7
- Association of slower linear growth with verbal intelligence quotient score <70 at age 7 years:
  - Slower linear growth by Olsen reference: aOR, 3.5[a]; 95% CI, 1.1–12.7
  - Slower linear growth by INTERGROWTH-21st: aOR, 2.0; 95% CI, 0.5–9.9

Choose a growth curve that represents your population.

a. $P < .05$

Why is it important to achieve normal growth rates in preterm infants?

Growth Faltering Increases the Incidence of Pathological Outcomes[a]

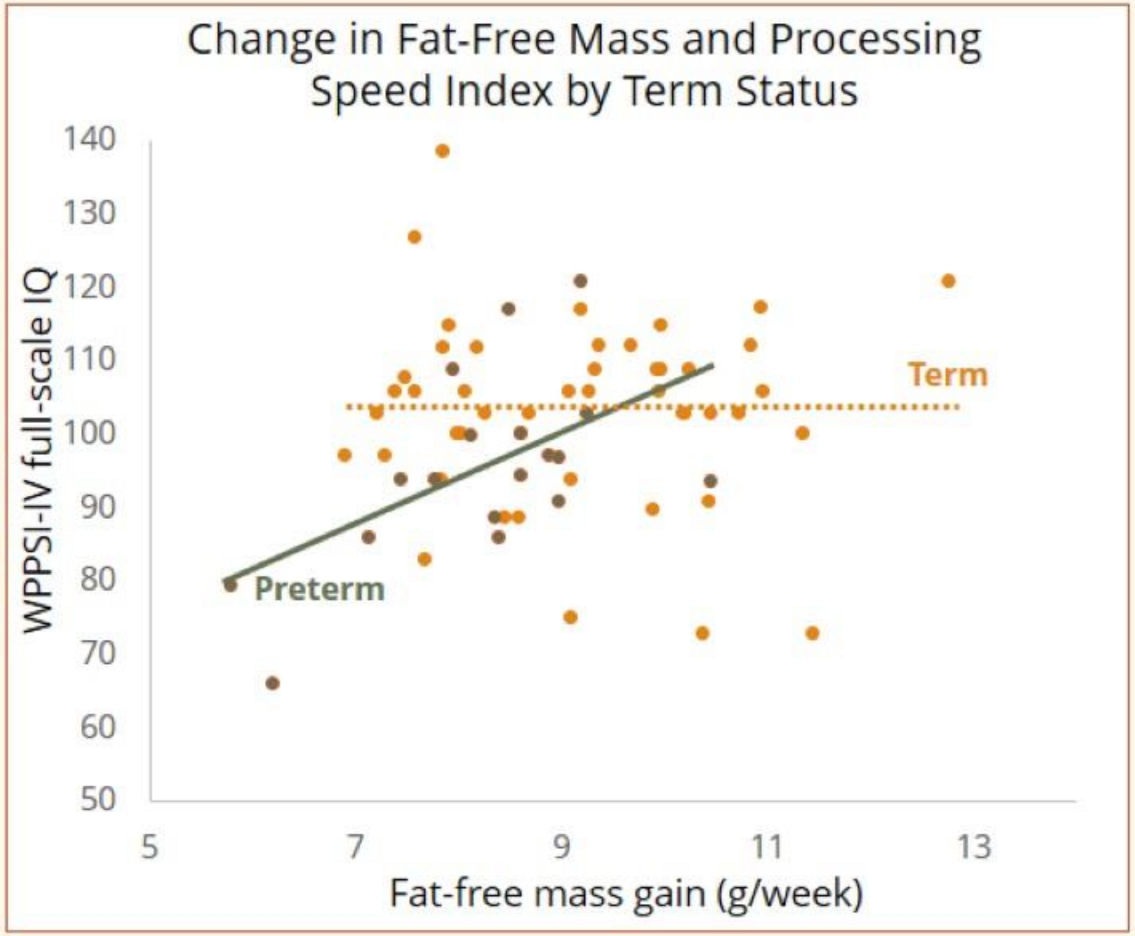


a. In a study of 1493 preterm infants from the EPIPAGE cohort, following the growth curve was defined as birth weight >-2 standard deviations.
b. $P < .001$.
c. $P = .03$.

Guellec I, et al. *J Pediatr*. 2016;175:93-99.e1.

Achieving Optimal Growth in Preterm Infants Uniquely Enhances Long-Term Outcomes—because they are in critical stages of development

- In preterm infants, fat-free mass gains from term to 3–4 months (corrected age) were positively associated with cognition at age 4 years
- In term infants, no such association was identified
- Therefore, nutritional status in the first months after birth may influence long-term neurodevelopmental and cognitive outcomes for preterm infants



Ramel S, et al. *J Pediatr*. 2016;173:108-115.

Risk Factors for Preterm Infant Growth Faltering

Risk factors we cannot control

- Lower birth weight or younger gestational age
- Male sex
- Comorbid diseases and required treatments (eg, mechanical ventilation, steroids, diuretics, and catecholamines, all of which are catabolic)
- Intrauterine growth restriction

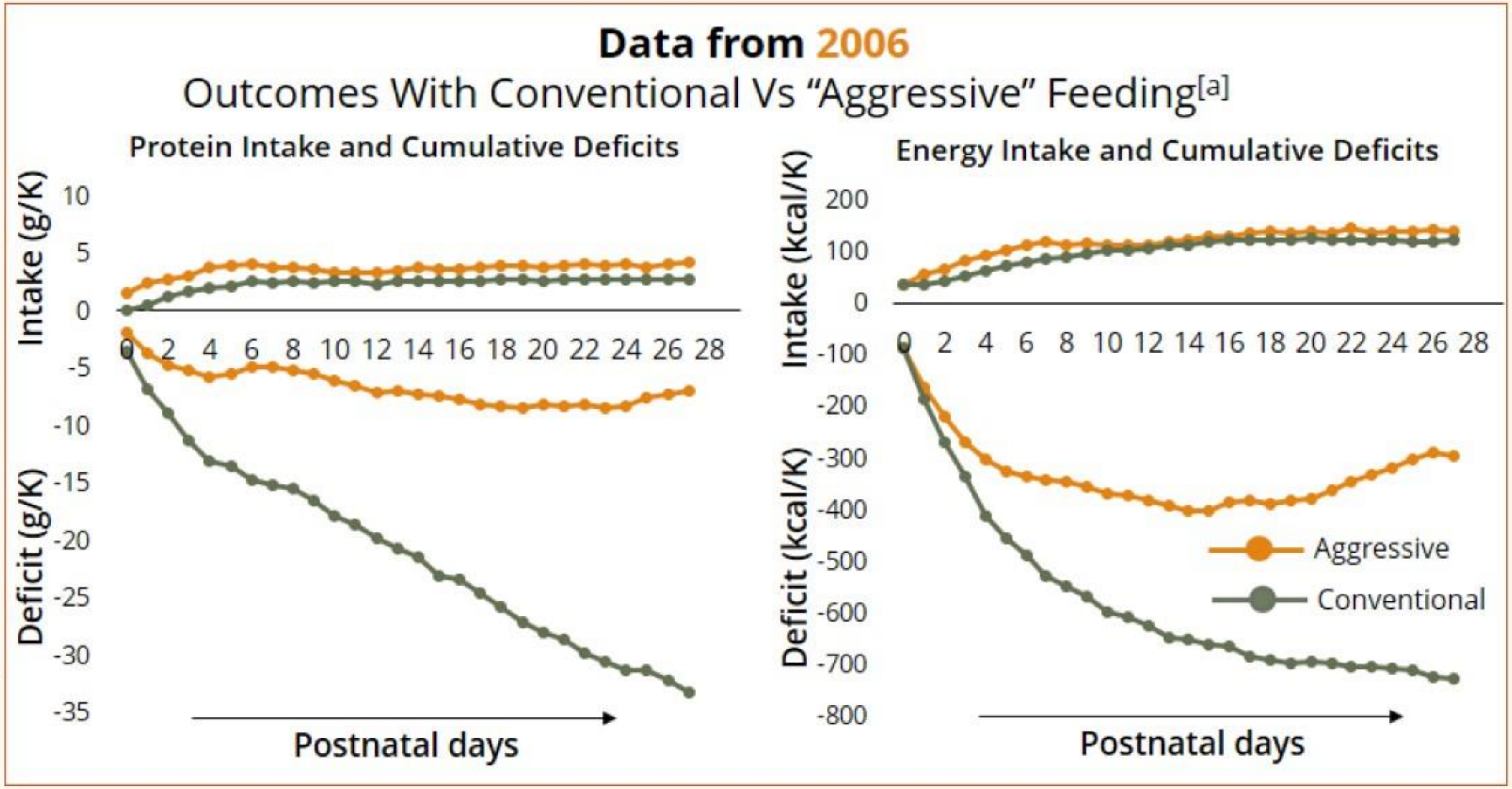
Risk factor we CAN control

- Underfeeding (low protein and energy intakes)

Clark RH, et al. *Pediatrics*. 2003;111(5):986. Figueras-Aloy J, et al. *Eur J Pediatr*. 2020;179:1469-79.

Even With Early and Aggressive Protein and Energy Intake, Cumulative Deficits in Nutrient Supply Still Occur

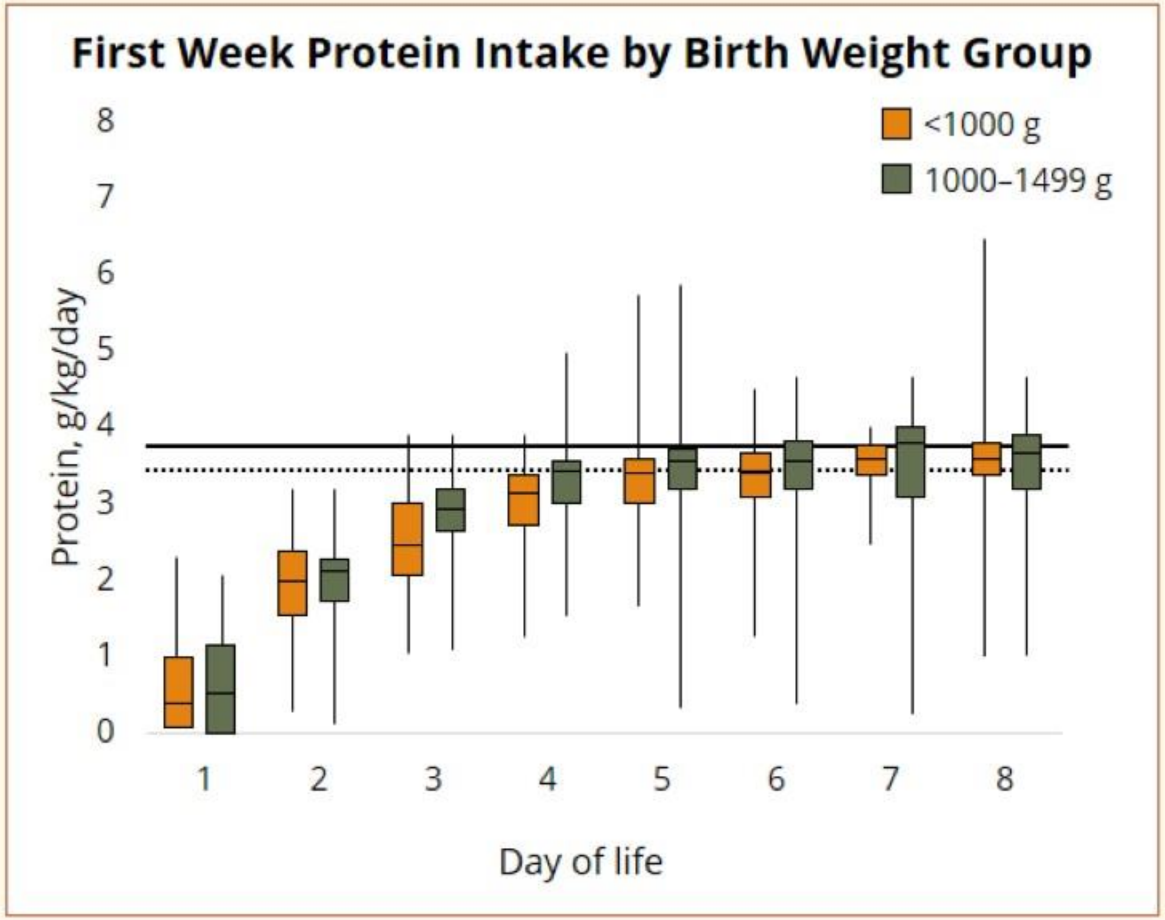
- The aggressive feeding schedule included several interventions, such as immediate initiation of 10% amino acid solution at 1.5 g/kg/day
- The aggressive feeding regimen was associated with lower rates of nutrient deficits
- **NOTE:** Even with a so-called aggressive regimen in this study, under nutrition occurred, albeit at a lower rate

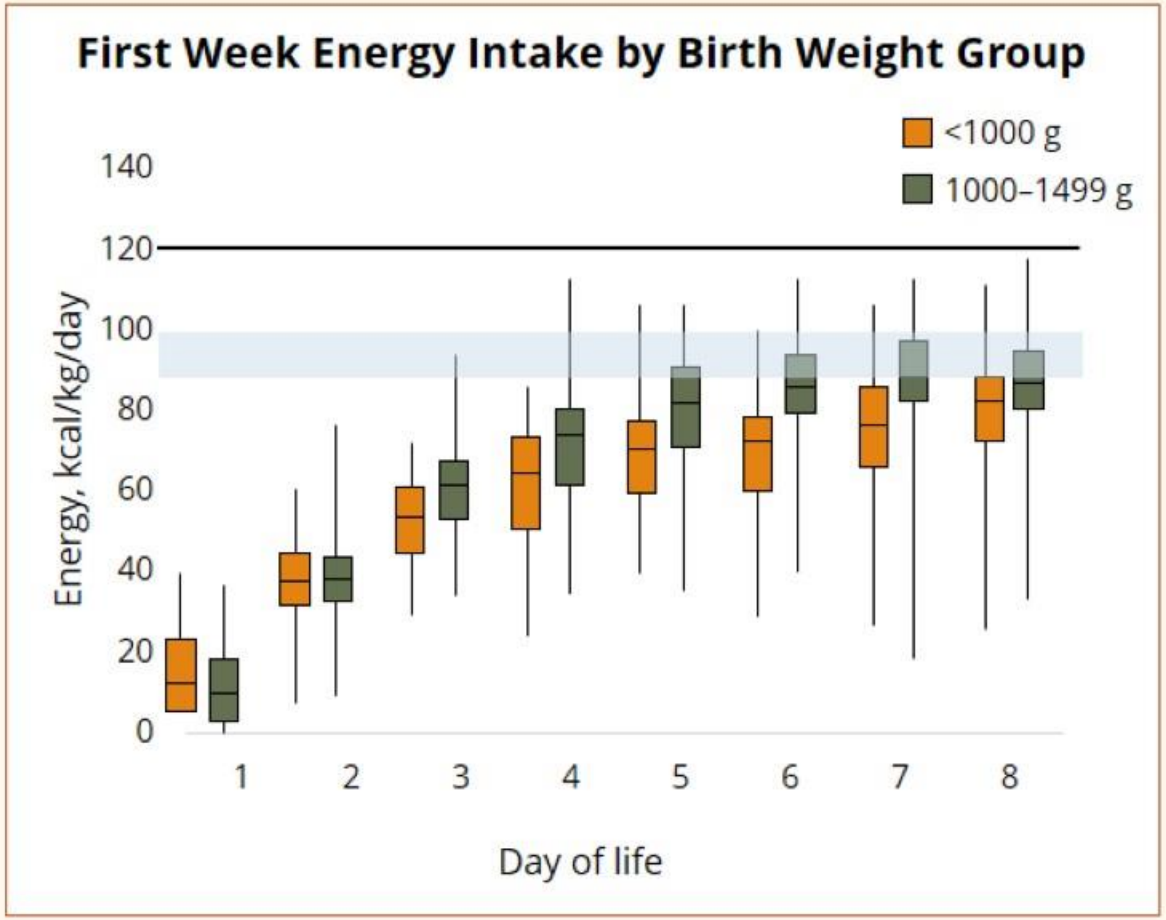


a. In a cohort of 117 VLBW infants, patients received aggressive feeding (1.5 g/kg/day amino acids plus 5.6 mg/k/min glucose, increased to 4 g/kg/day and 13 mg/kg/min, respectively; lipids started at 0.5 g/kg/day and increased to 3.5 g/kg/day). These outcomes were compared with a cohort of 65 VLBW infants who were conservatively fed.

Dinerstein A, et al. *J Perinatol*. 2006;26(7):436-442.

And Deficits in NICU Nutrition Practices Persist (**2017** Data), Especially in the First Week After Birth, Despite the Importance of Optimal Nutrition in Preterm Infants





Ng DV, et al. *JPEN J Parenter Enteral Nutr*. 2017;41(3):500-506.

Nutritional Needs for Preterm Infants

Nutritional Needs for Preterm Infants: Macronutrients

Amino Acids and Proteins

- Major functional and structural components of all cells
- Standardly, amino acids are delivered in parenteral solutions and intact proteins are delivered in formula (up to 3.5–4.5 g/kg/day for very preterm infants)

Total Energy

- 110–130 kcal/kg/day (enteral) and 85–95 kcal/kg/day (parenteral)

Lipids

- Major energy reserve at birth and provide majority of energy needs (3.5 g/kg/day)
- Fundamental for brain growth and development

Carbohydrates

- Support basal metabolism
- IV dextrose infusion starting at 4–5 mg/min/kg, adjusted early and frequently in response to glucose concentration measurements to avoid hypo- and hyperglycemia

Wight N, et al. Nutritional Support of the Very Low Birth Weight (VLBW) Infant. 2018. Accessed September 15, 2020. https://www.cpqcc.org/sites/default/files/pdf/toolkit/Nutritional%20Support%20of%20the%20VLBW%20Infant_QI%20Toolkit_September%202018_FINALv3%20(reduced%20size).pdf.

Role of Protein in Growth and Development

Proteins Are Not Only Important for Weight Gain But Also for Optimal Body Composition

- Growth of lean, fat-free body mass is dependent on protein intake in preterm infants
  - This includes muscle, but also brain, bone, and organ mass
- Studies have shown that lean body mass is lower in preterm infants than in term infants, and invariably lower in infants who had IUGR

MRI-Determined Weight, Adiposity, and Body Mass Fractions[2]

	Term (n = 10)	Former preterm (n = 15)
Body weight, g	3094	**2519** [a]
Lean body mass, g	2417	**1935** [a]
Absolute fat mass, g	691	594
Adiposity	24.5%	26.2%

a. $P < 0.05$

1. Hay WW, Thureen P. *Pediatr Neonatol*. 2010;51(4):198-207.
2. McLeod G, et al. *J Paediatr Child Health*. 2015;51(9):862-869.

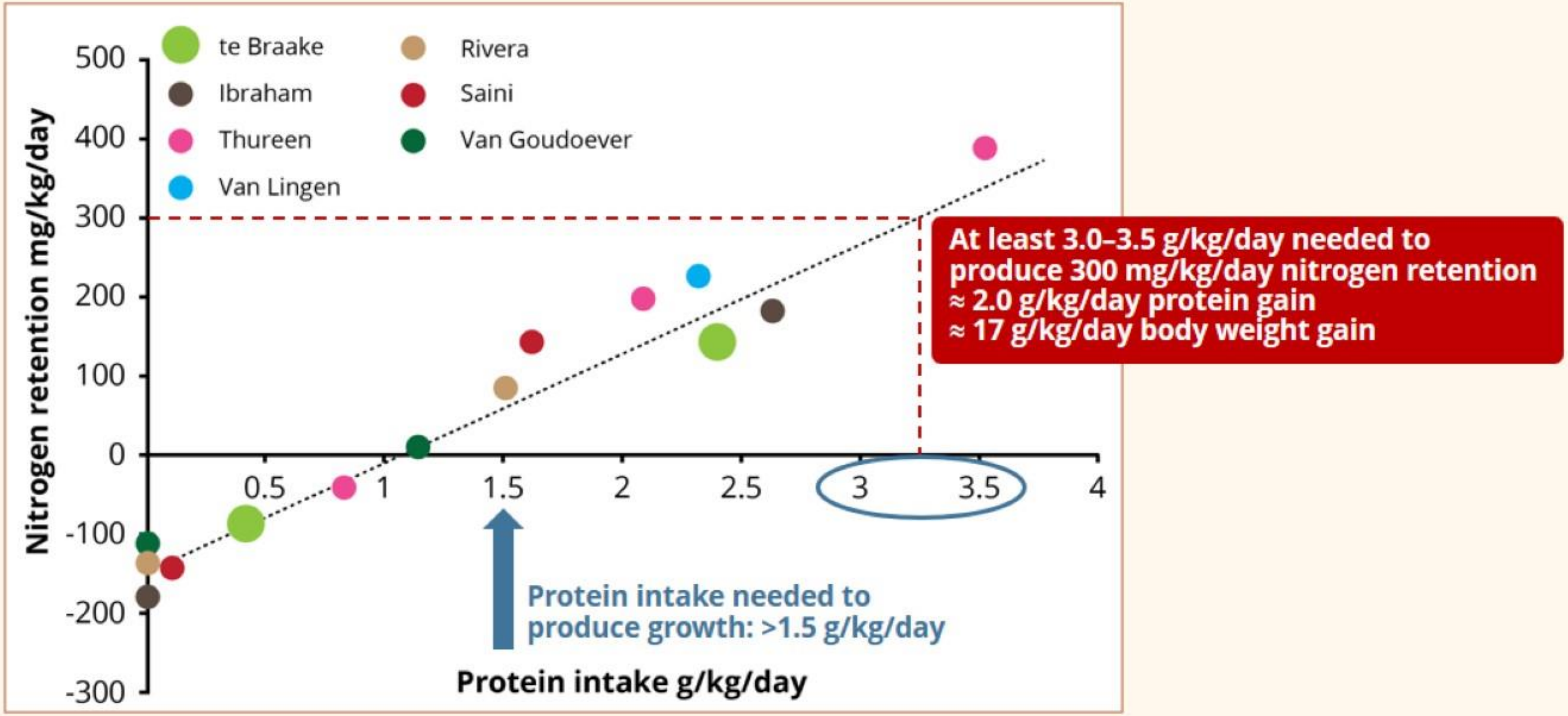
Higher Protein (and Energy) Intake in the First Week of Life Is Associated With Better Long-Term Neurodevelopmental Outcomes

- Every **1 g/kg/day increase in protein** intake during the first week associated with an **8.2-point increase in Bayley MDI** at 18 months
- Every **10 kcal/kg/d increase in energy** intake during the first week associated with a **4.6-point increase in MDI** at 18 months
- Conflicting results of longer-term outcome studies underscore the importance of prospective studies with continued follow-up

Stephens BE, et al. *Pediatrics*. 2009;123(5):1337-1343. Tottman AC, et al. *J Pediatr Gastroenterol Nutr*. 2020;70(1):72-78.

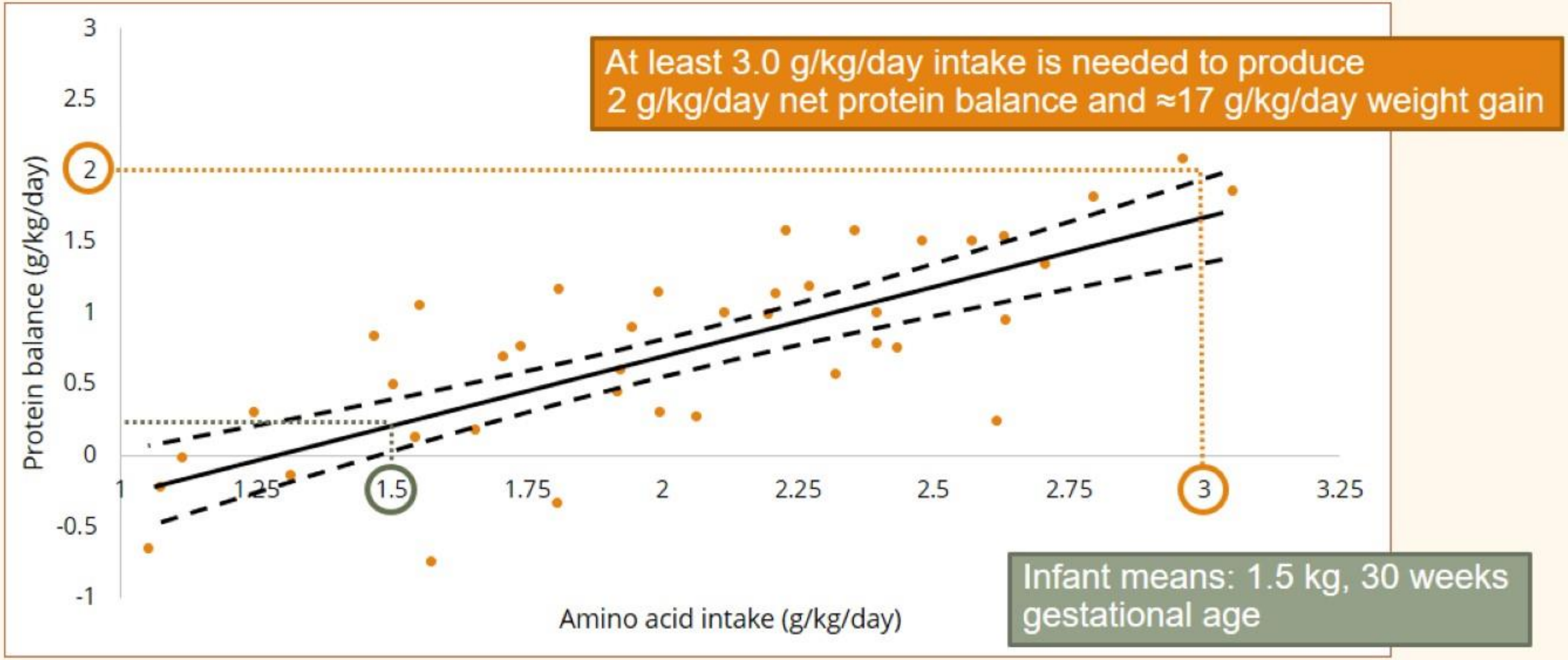
Protein Needs of Preterm Infants

Across Many Studies, Data Support That Failure to Provide Early Dietary Protein Results in Negative Nitrogen Balance



Embleton ND. *Early Hum Dev.* 2007;83(12):831-837.

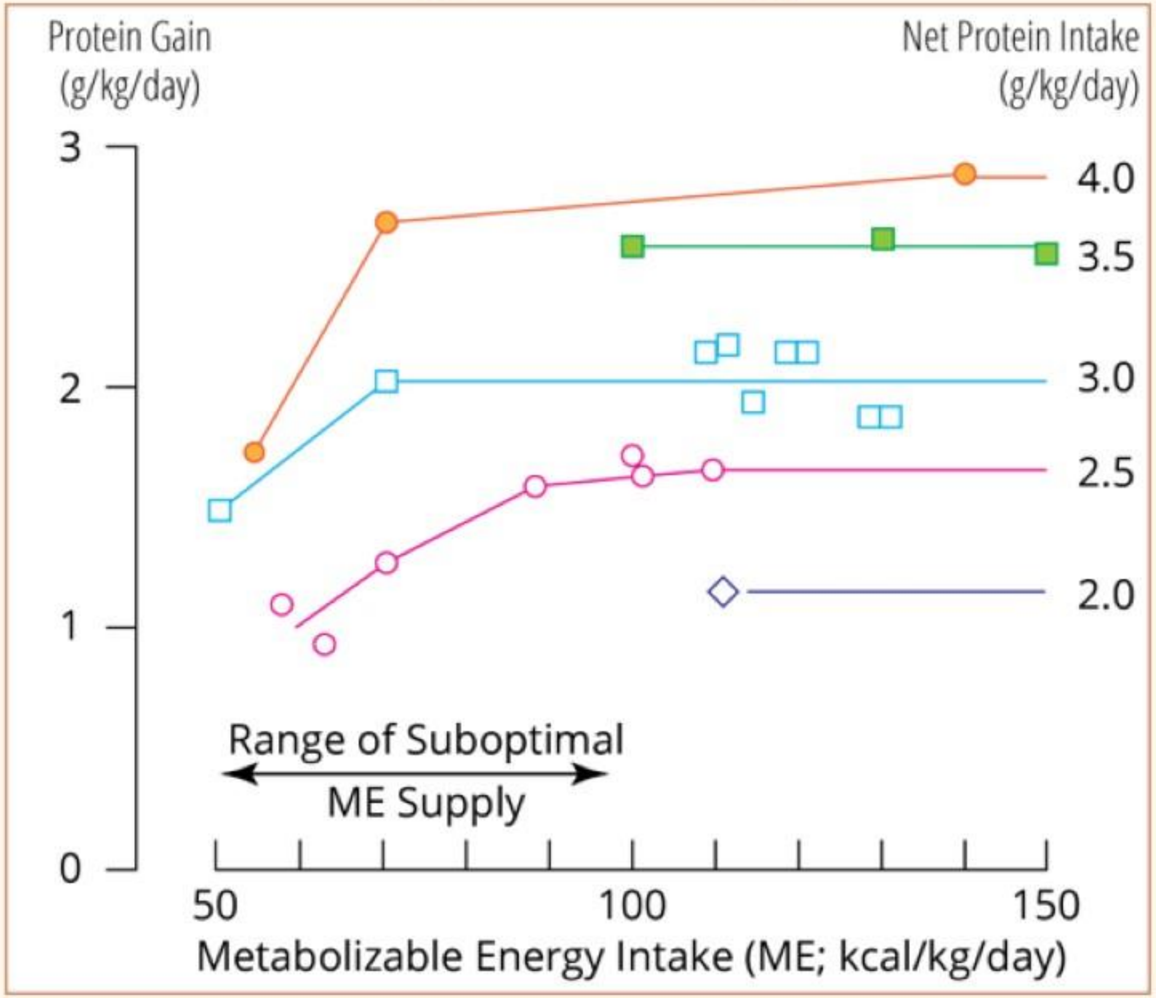
Even Right After Birth, There Is a Direct Correlation Between Amino Acid Supply and Protein Balance Through at Least 3 g/kg/day



1. Thureen PJ, et al. *Am J Clin Nutr.* 1998;68(5):1128-1135.
2. Thureen PJ, et al. *Pediatr Res.* 2003;53(1):24-32.

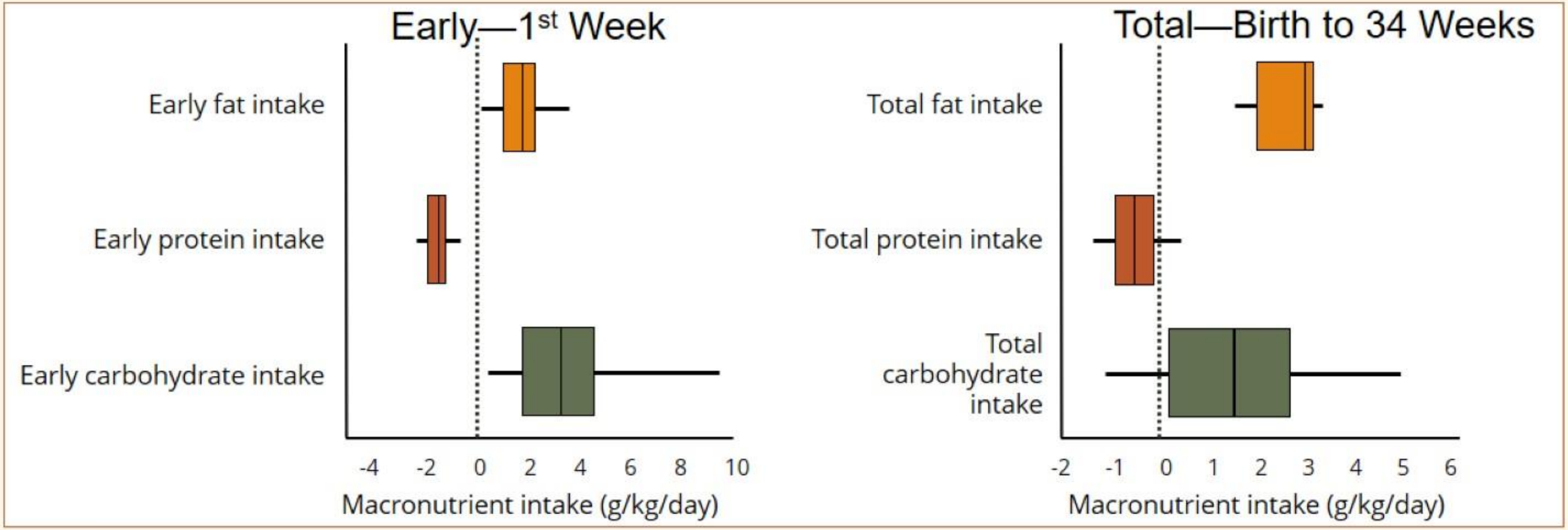
Although Protein Synthesis and Gain Require Energy, Protein Synthesis and Gain Plateau at High Energy Intakes

- Energy intake above sufficient levels does not increase protein synthesis or gain
- Sufficient energy intake:
  - At least 85 nonprotein kcal/kg/day IV
  - At least 110 nonprotein kcal/kg/day enteral
- **Once energy intake is sufficient, protein synthesis and gain are dependent on protein intake**



Hay WW Jr., *Pediatr Gastroenterol Hepatol Nutr*. 2018;21(4):234-247.
Micheli J, et al. Protein, pp 29–46 in Tsang RC, et al (eds). *Nutritional Needs of the Preterm Infant*. Williams & Wilkins. 1992.

Nutrition Is Frequently Imbalanced in the NICU, Favoring Carbohydrates and Lipid Over Protein



Diets excessively high in carbohydrates and fat can lead to infants with:

- Higher body fat mass
- Less muscle mass
- Shorter stature
- Higher risk for neurodevelopmental deficits

Vasu V, et al. *Int J Obes (Lond).* 2013;37(4):500-504.

Protein Needs of Preterm Infants

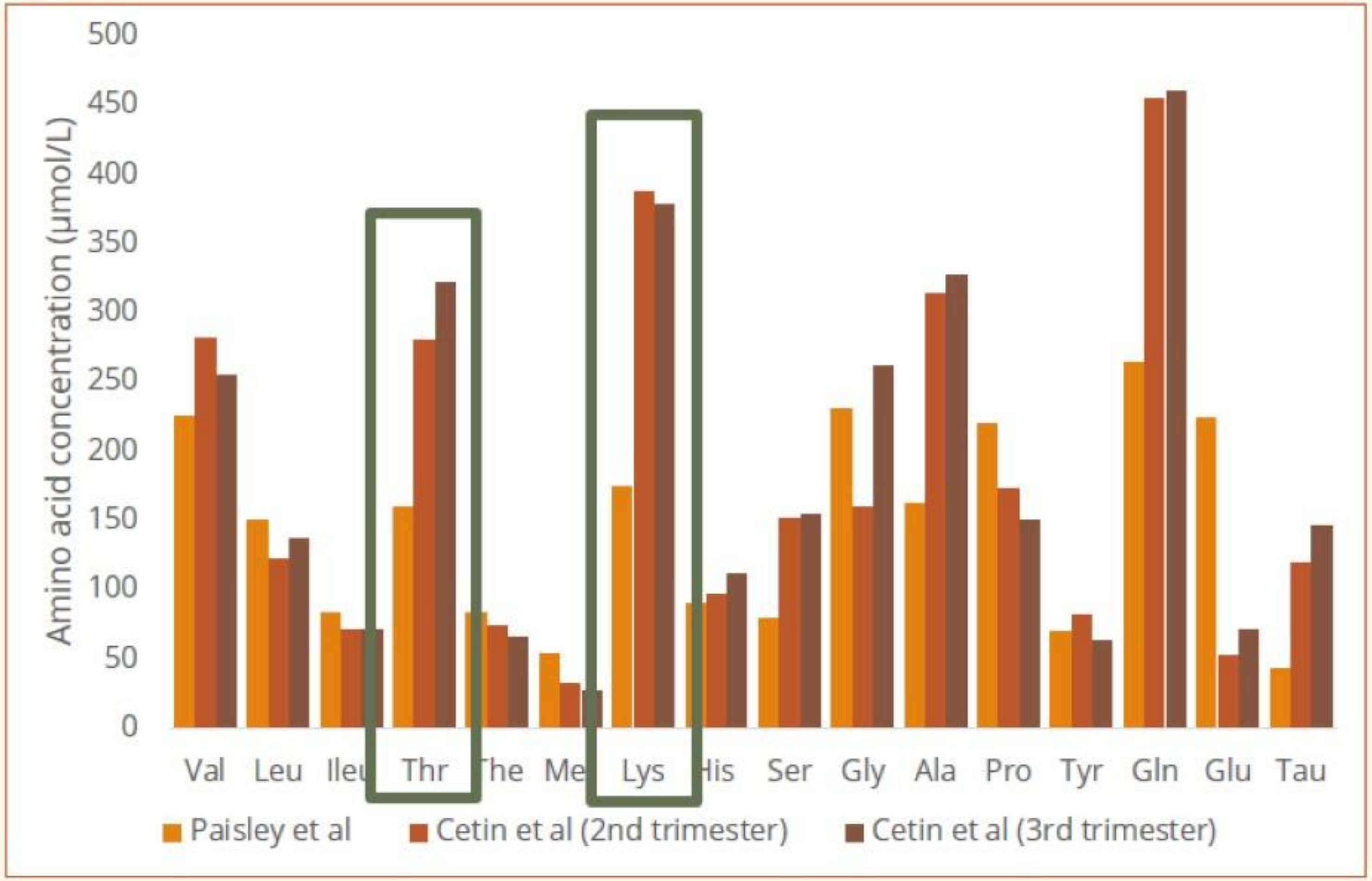
Parenteral

Recommendations for **Parenteral** Protein Intake in Preterm Infants

- **Early postnatal days:** 2.5–3.5 g/kg/day
- **Following days:** titrate up to 3.5 g/kg/day (ESPGHAN) or 4.0 g/kg/day (US)
- Ensure protein intake is accompanied by nonprotein intakes of >85 kcal/kg/day and adequate micronutrient intake (day 2+)
- 30–40 kcal per 1 g amino acids to ensure amino acid utilization, but only up to 120–130 kcal/kg/day total energy

Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. Karger; 2014.
van Goudoever JB, et al. *Clin Nutr*. 2018;37(6):2315-2323.

There Also Is Need to Improve IV Amino Acid Solutions, as a Lack of Essential and Conditionally Essential Amino Acids Could Negatively Impact Studies Assessing Protein Administration and Growth



Suboptimal levels of even 1 essential amino acid could limit net protein balance and growth.

Administering more of an unbalanced amino acid solution does not guarantee optimal plasma amino acid concentrations.

1. Thureen PJ, Hay WW. *Semin Neonatol.* 2001;6:403-415.
2. Morgan C, Burgess L. *JPEN J Parenter Enteral Nutr.* 2017;41(3):455-462.

Protein Needs of Preterm Infants

Enteral

Recommendations for **Enteral** Protein Intake in Preterm Infants

- **For very preterm, VLBW infants:** 3.5–4.0 g/kg/day
- **By late preterm age:** taper down to 2.5–3.0 g/kg/day
- **At term age:** taper down to 2–2.5 g/kg/day (similar to normal breast feeding intakes of mother's own milk)
- **Catch-up growth (for infants who had prolonged under nutrition due to illnesses):** up to 4.5 g/kg/day (although no evidence that >4.0 g/kg/day actually enhances growth)

Despite These Recommendations, Current Diets in Preterm Infants Do Not Promote Sufficient Brain Growth

Figure. **Brain Volumes by MRI Plotted Against GA in Preterm and Fetal Cohorts**

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Preterm infant brain growth is slower in all regions compared with growth in the normally growing fetus.

GA, gestational age; MRI, magnetic resonance imaging; TBV, total brain volume; ICV, intracranial cavity volume.

Bouyssi-Kobar M, et al. *Pediatrics.* 2016;138(5):e20161640.

What Diet Does Promote Brain Growth?

- Compared with early parenteral protein intake, **enteral** feeding and early lipid and energy intakes are critical for preterm brain development
- According to MRI studies, higher **cumulative** intakes of fat and total energy, as well as **cumulative** protein intake, were positively associated with:
  - White matter microstructure
  - Total brain volume
  - Regional brain volumes

Cumulative macronutrient (protein and energy) intake, rather than average, is the most important determinant for improved brain development

Ottolini KM, et al. *Pediatr Res.* 2020;87(2):194-201.

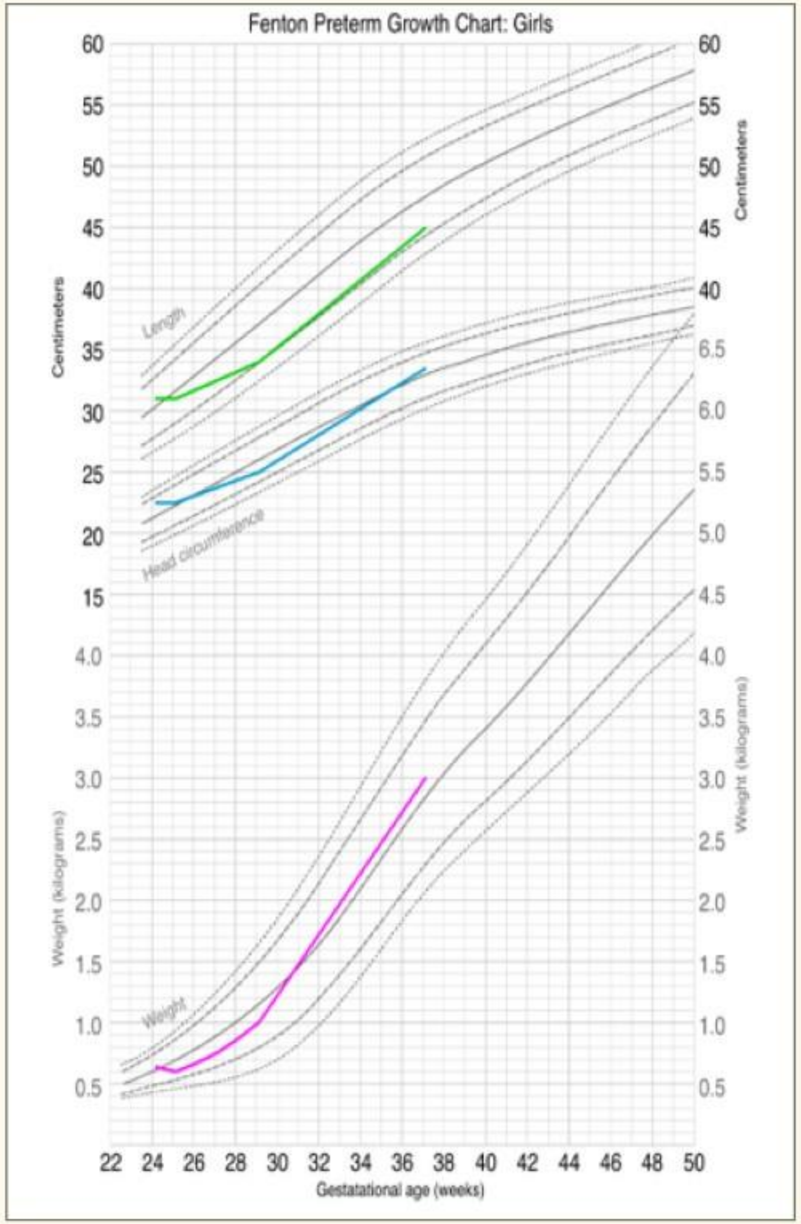
Case Study:
Ex-24-Week Infant, Now Corrected to 37 Weeks

- **Problems:**
  - PDA
  - Pulmonary immaturity
  - Anemia of prematurity
  - Apnea of prematurity
  - Pulmonary HTN
  - ROP
  - S/p catheter-placed plug of PDA
  - Bronchopulmonary dysplasia
- **Respiratory Support:**
  - NIPPV
- **Medications:**
  - Furosemide
  - Sodium and potassium
  - Hydrochlorothiazide
  - Spironolactone
  - Hydrocortisone
  - Multivitamin and iron infant and toddler supplement

HTN, hypertension; NIPPV, noninvasive positive-pressure ventilation; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

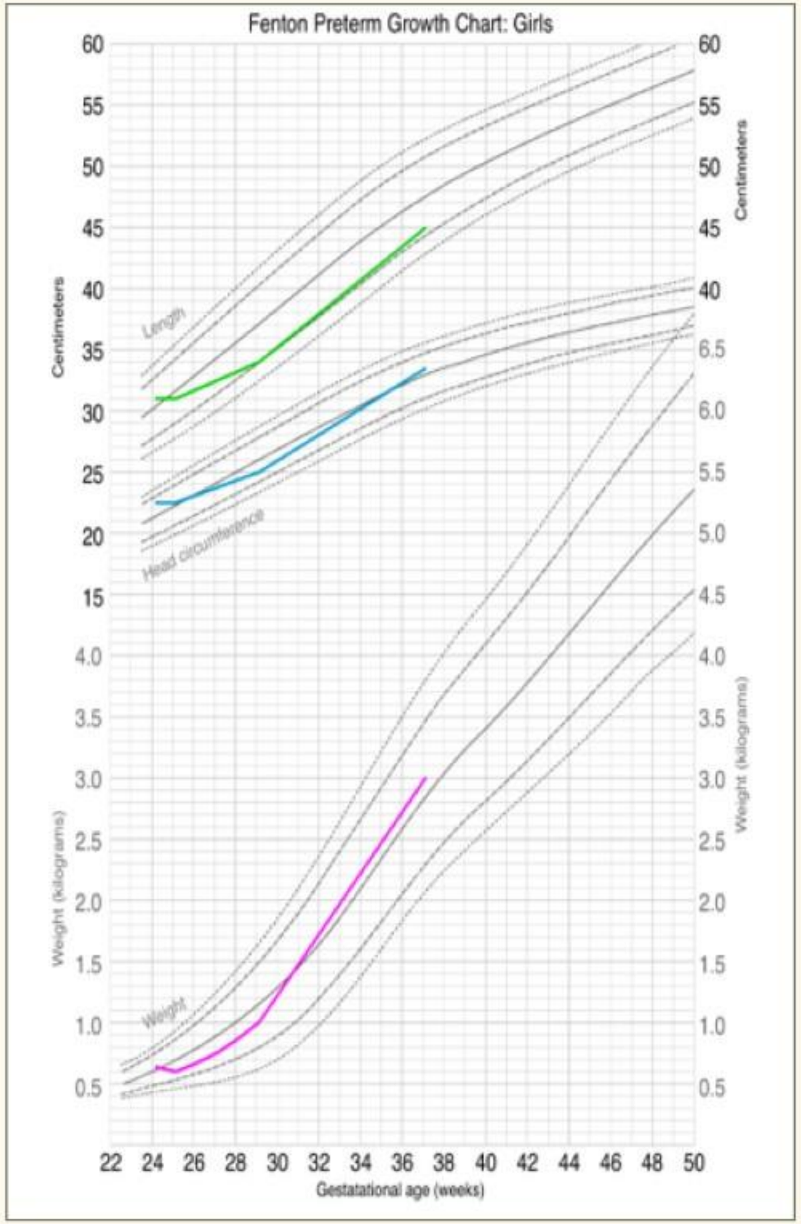
Case Study

- Weight-for-age:
  - 3 kg; 64th %ile, Z +0.35
  - Crossed birth percentile around 31 weeks CGA
  - 33–37 weeks: ~35 g/d
- Length:
  - 45 cm; 15th %ile, Z -1.03
  - Initially experienced a deceleration; has not regained birth percentile
  - 33–37 weeks: 1.2 cm/wk
- Head Circumference:
  - 33.2 cm; 57th %ile, Z +0.18
- BMI (Olsen):
  - 98th %ile, Z+1.99
  - Estimated ideal body weight: 2.35 kg
- Physical Exam;
  - No signs or symptoms of edema or fluid overload
  - Increased fat mass



Case Study

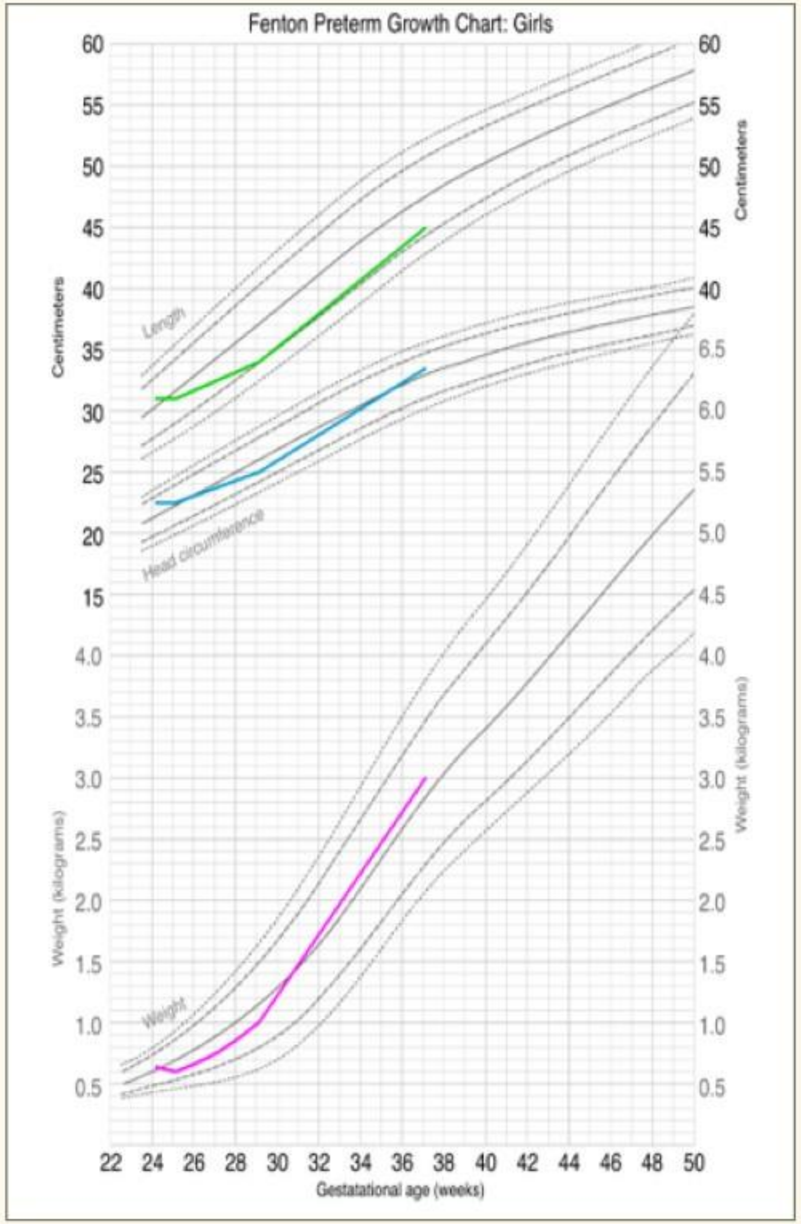
- Current nutrition:
  - MM with HMF to 24 kcal/oz at ~150 mL/kg/day
  - Preterm high-protein formula 24 kcal/oz used as backup for approximately half of feedings
  - Estimated intake provides:
    - » 120 kcal/kg/day
    - » 3.9 g/kg/d protein
- Nutrition intervention:
  - Estimated needs: 95–110 kcal/kg/day, 3 g/kg/d protein
    - » Start with reduction of calories to 110 kcal/kg/day
    - » MM with HMF to 22 kcal/oz or Preterm Formula at 22 kcal/oz to provide 110 kcal/kg/day and 3 g/kg/d protein
  - Goal anthropometrics
    - » Weight: 20–25 g/d
    - » Length: 1.2–1.5 cm/wk



HMF, human milk fortifier; MM, maternal milk.

Case Study

- Recommended screening:
  - Electrolytes (hydration status, protein markers, etc)
  - Phosphorus, alkaline phosphatase, vitamin D
    - » May need additional calcium, phosphorus and vitamin D supplementation in light of decreased fortification
  - Iron status
- Assessment:
  - Imbalance of nutrients caused disproportionate growth
  - Comorbidities and polypharmacy impacts growth and nutrition
  - Overfeeding and accumulation of excessive fat mass can make development and progression towards less support more difficult
- Monitoring:
  - Measure length weekly with a length board
  - Physically assess the patient to trend body habitus
  - Adjust energy needs as infant's metabolic demands change (ie, weaning respiratory support, increased PO intake, etc)

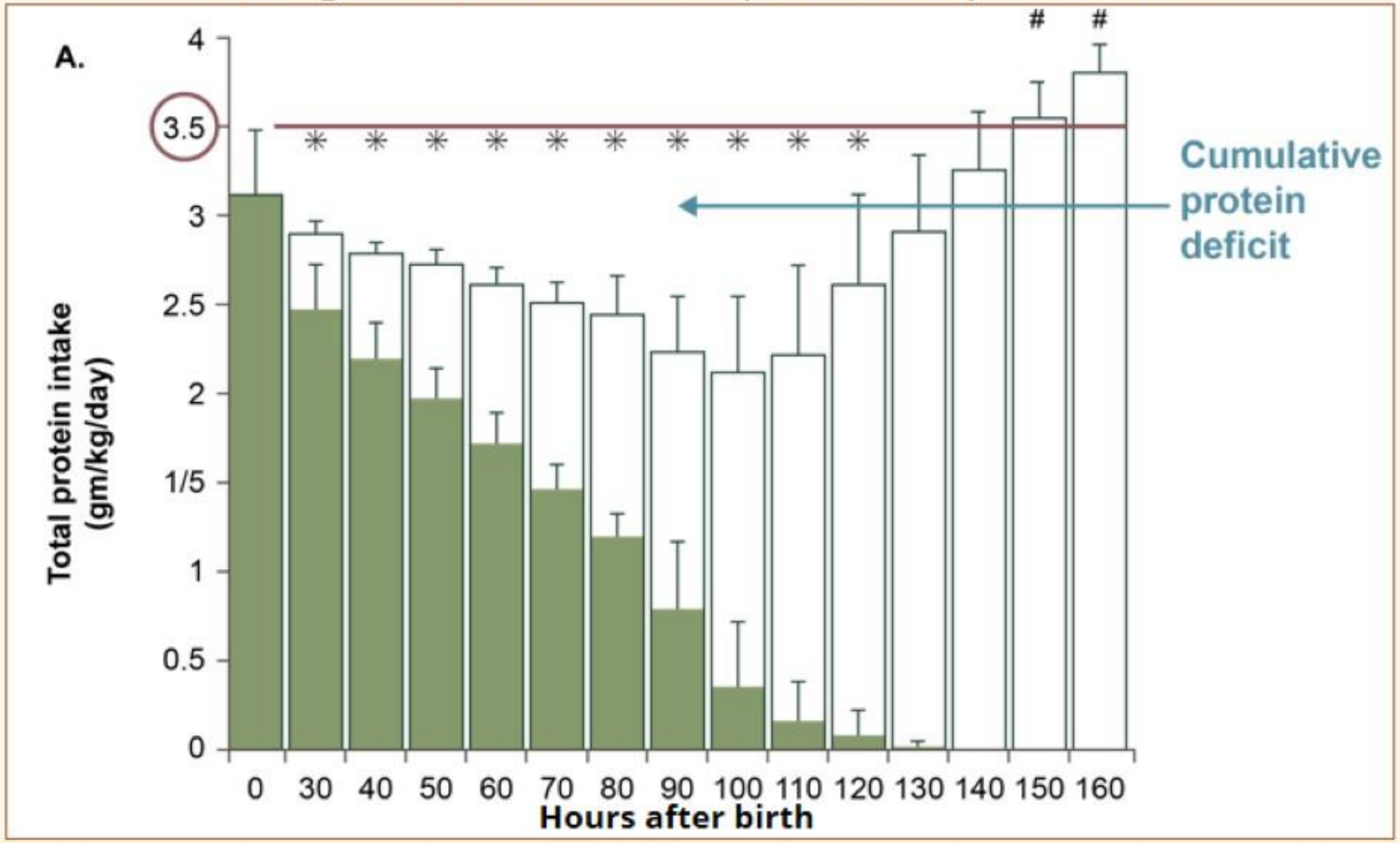


Protein Needs of Preterm Infants

Parenteral to Enteral Transition

During the Parenteral to Enteral Transition, Malnutrition Can Develop Easily

Because total protein intake can fail to meet requirements when parenteral nutrition is weaned but enteral nutrition is not advanced fast enough to maintain total protein requirements.



Miller M, et al. *J Parent Ent Nutr.* 2014;38:489-497.

Ensuring Optimal Protein Intake Requires Adjusting Dosing According to Gestational Age

Between 24 and 30 weeks

- Protein requirements: 3.5–4.0 g/kg/day

Between 32 and 37 weeks

- Fractional growth rate decreases, as does the protein requirement for growth
- Protein requirements: 2.5–3.5 g/kg/day

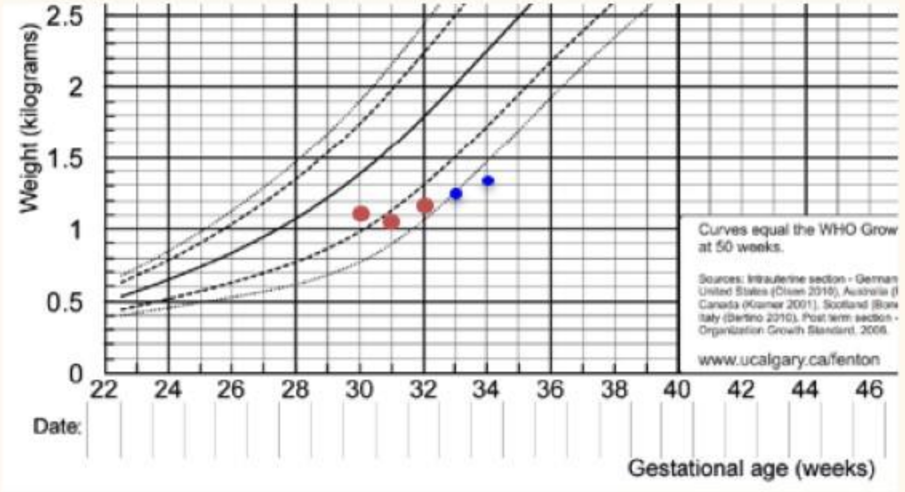
At term

- Protein requirements decrease to those of the normal breast fed infant
- Protein requirements: 1.5–2.0 g/kg/day

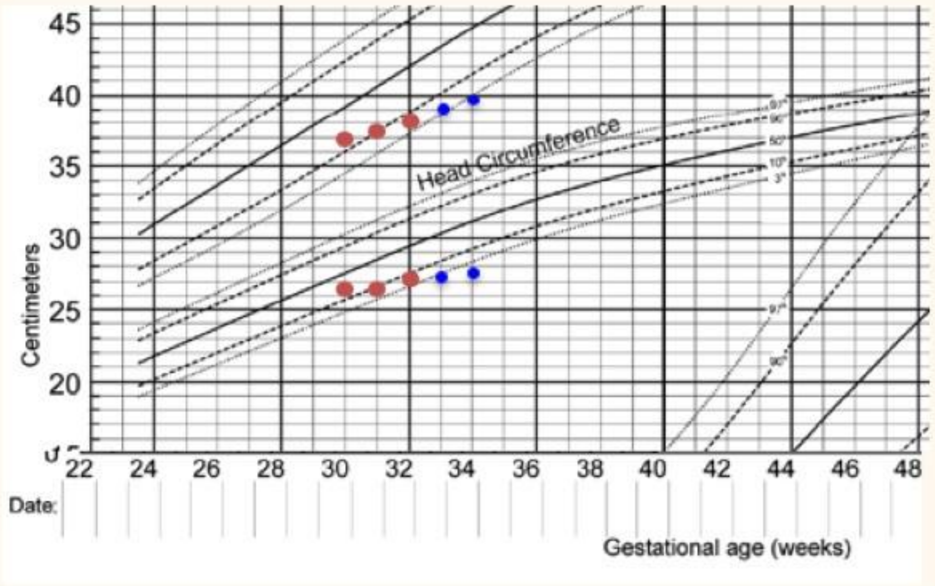
Hay WW Jr., *Pediatr Gastroenterol Hepatol Nutr.* 2018;21(4):234-247.

Case Study: 30-Week-Old Male

- Born via cesarean delivery due to cord prolapse
- Apgar scores, 7, 9
- Required PPV in delivery room and transitioned to CPAP after a few minutes



- **DOL 1:** Started on PN
- **DOL 2:** Started maternal/donor milk
- **DOL 6:** Rec'd fortification with HMF to ~22 kcal/oz at ~40 mL/kg/day; continued to advance enteral volume
- **DOL 10:** PN d/c'd d/t access issues
- **DOL 11:** Maternal milk supply depleted; receiving all donor milk
- **DOL 12:** Fortification increase to 24 kcal/oz with HMF at volume of 160 mL/kg/day (estimated to provide ~125–130 kcal/kg/day and 4 g/kg/d protein)
- **DOL 14:** all growth parameters have declined from birth; BUN of 4 mg/dL, all electrolytes WNL
  - Wt: regained BW on DOL 8; gain of 7 g/kg/day thereafter
  - L: Increase 0.6 cm/wk x 2 weeks (goal: 1–1.5 cm/wk)
  - HC: Increase 0.5 cm/wk x 2 weeks (goal: 1 cm/wk)

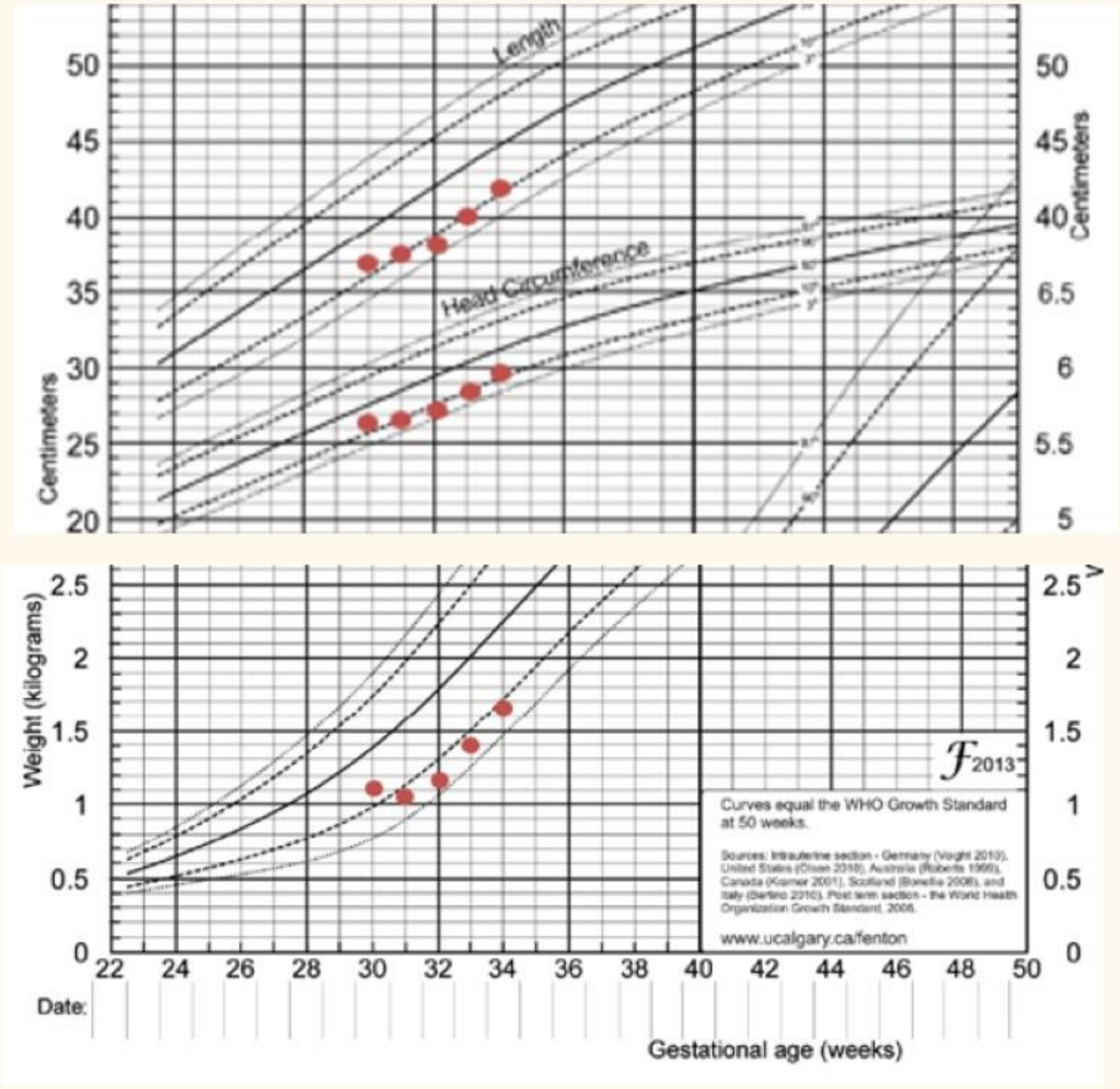


BW, body weight; CPAP, continuous positive airway pressure; DOL, day of life; HC, head circumference; L, length; PPV, positive-pressure ventilation.

Case Study

- **DOL 14:**
  - Maternal milk is no longer available
  - Receiving all fortified donor human milk
  - Additional protein supplement added to provide an extra 0.5 g/kg/day protein
- **DOL 21:** weekly change
  - Wt: 33 g/kg/day or 43 g/d, +0.26 Z-score
  - L: Increase 1.5 cm, +0.04 Z-score (goal: 1–1.5 cm/wk)
  - HC: Increase 1.2 cm, +0.22 Z-score (goal: 1 cm/wk)
- **DOL 28:** weekly change
  - Wt: 22 g/kg/day or 35 g/d, +0.06 Z-score
  - L: Increase 1.5 cm, +0.06 Z-score (goal: 1–1.5 cm/wk)
  - HC: Increase 1.3 cm, +0.3 Z-score (goal: 1 cm/wk)

Age	Weight (g)	Length (cm)	HC (cm)
Birth (30 w)	1100 (17th %ile, Z -0.94)	37 (19th %ile, Z -0.88)	26.5 (24th %ile, Z -0.71)
DOL 7 (31 w)	1050 (7th %ile, Z -1.5)	37.5 (11th %ile, Z -1.23)	26.5 (9th %ile, Z -1.34)
DOL 14 (32 w)	1150 (5th %ile, Z -1.68)	38.5 (8th %ile, Z -1.38)	27 (5th %ile, Z -1.61)
DOL 21 (33 w)	1450 (8th %ile, Z -1.42)	40 (9th %ile, Z -1.34)	28.2 (8th %ile, Z -1.39)
DOL 28 (34 w)	1695 (9th %ile, Z -1.36)	41.5 (10th %ile, Z -1.28)	29.5 (14th %ile, Z -1.09)



Protein Sources for Preterm Infants

Protein Sources for Preterm Infants

	Preterm mother's own milk (MOM)	Donor human milk	Preterm formula (bovine milk-based)
Calories, kcal/100 mL	68	67	74
Protein, g/100 mL		0.9	2.1
Days 1–3	2.7	↓	↓
Days 4–7	1.6		
Week 2	1.3		
Week 3–4	1.1		
Fortification	Needed	More needed than MOM given low protein content	Concentrate as needed
Bioactive components (eg, immune cells, growth factors)	Present	Present but reduced by processing and pasteurization	Absent

Shulhan J, et al. *Adv Nutr*. 2017;8(1):80-91.

Compared With Unfortified Donor Breast Milk, Feeding With Formula May Result in Increased Growth Outcomes in Preterm Infants, but at the Risk of Increased Rates of NEC and With No Benefit for Better Neurodevelopment

Moderate-quality evidence suggests that in preterm and LBW infants, formula feeding compared with donor human milk feeding resulted in:[1]

- Higher rates of in-hospital weight gain
- Higher rates of linear and head growth
- Higher risk of necrotizing enterocolitis
- No better effect on long-term growth or neurodevelopment

But there is no difference in growth outcomes when breast milk (mother's own milk) is fortified.[2]

NEC, necrotizing enterocolitis; LBW, low birth weight.

1. Quigley M, et al. *Cochrane Database Syst Rev.* 2019;7:CD002971.
2. Soldateli B, et al. *J Perinatol.* 2020;40:1246-1252.

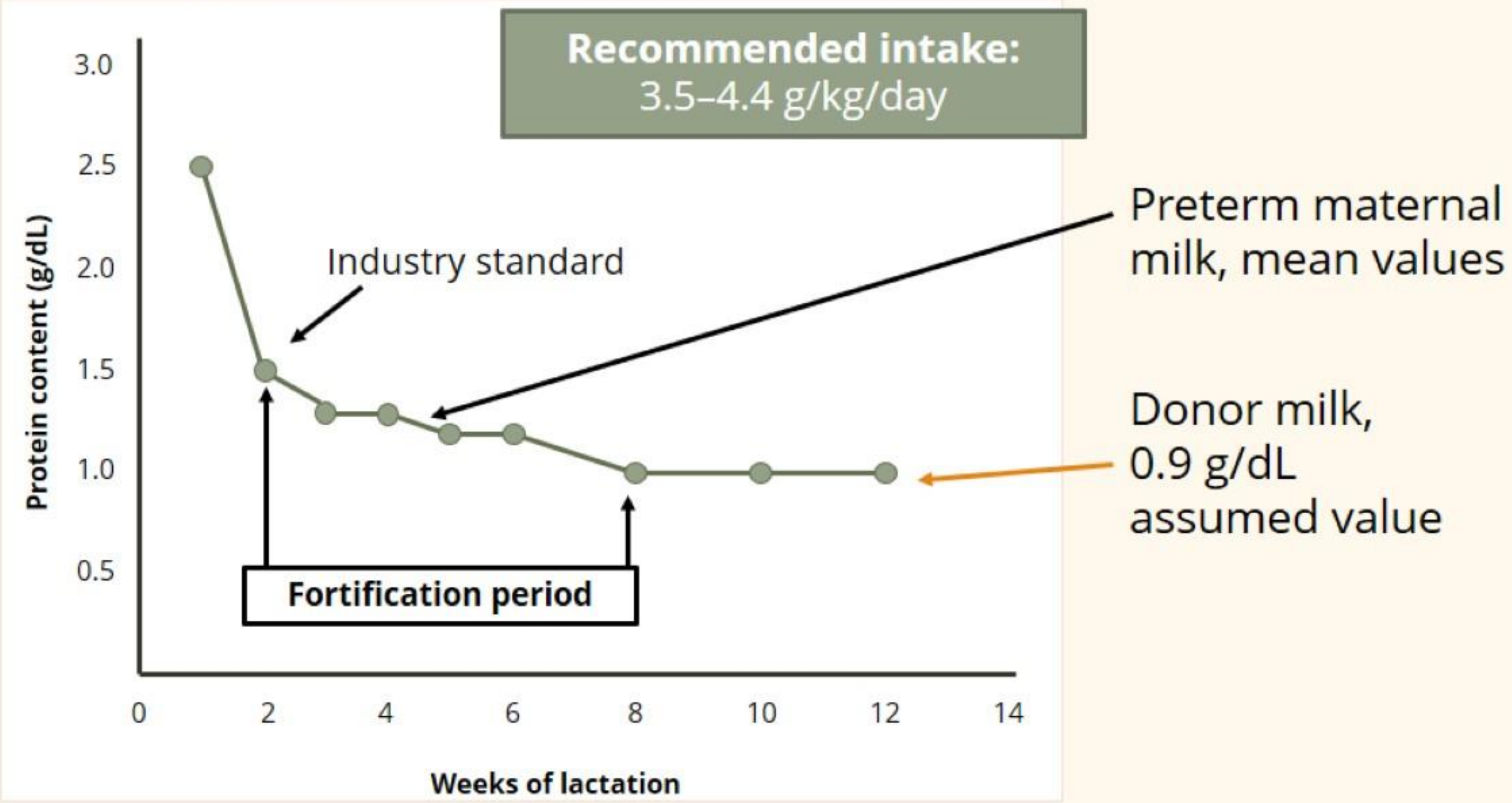
Increased Volumes of Human Milk and Formula May Increase Growth[a], But These Data Are in Infants Over 30 weeks PMA

	Higher volume (n = 104)	Usual volume (n = 113)	*P* value
Growth velocity, g/kg/day (mean ± SD)	20.5 ± 4.5	17.9 ± 4.5	<.001
Weight (g), mean ± SD (Z score, mean ± SD)	2365 ± 324 (-0.60 ± 0.73)	2200 ± 307 (-0.94 ± 0.71)	<.001
Head circumference (cm), mean ± SD (Z score, mean ± SD)	31.9 ± 1.3 (-0.30 ± 0.91)	31.4 ± 1.3 (-0.53 ± 0.84)	.01
Length (cm), mean ± SD (Z score, mean ± SD)	44.9 ± 2.1 (-0.68 ± 0.88)	44.4 ± 2.0 (-0.83 ± 0.84)	.04
Mid-arm circumference (cm), mean ± SD	8.8 ± 0.8	8.4 ± 0.8	.002
Weight <10th percentile at completion, n (%)	12 (12%)	24 (21%)	.07
Days on respiratory support, mean (range)	6 (0–85)	6 (0–85)	0.81
NEC ≥ stage 2, n (%)	0 (0%)	0 (0%)	1.00
Feeding intolerance, n (%)	2 (2)	3 (3)	1.00

a. In a randomized clinical trial of 224 LBW preterm infants, 104 infants received **180–200 mL/kg/day (higher volume feeds)**, and 113 infants received **140–160 mL/kg/day (usual volume feeds)**. MOM fortified after full volume feeds attained. Preterm formula was 24 kcal/oz.

Travers CP, et al. *J Pediatr.* 2020;224:66-71.e1.

Fortification Is Key for Human Milk, but Especially Donor Milk, in Very Preterm Infants



Radmacher PG, Adamkin DH. *Semin Fetal Neonatal Med.* 2017;22(1):30-35.

How Is Human Milk Fortified?

- **Blind fortification:** based on the assumption that human milk being fortified has protein content of 1.5 g/dL and energy content of 20 kcal/oz
  - Most widely used strategy
  - Nutrient content variation is not factored into fortification
  - Resulting milk probably has less protein and energy than the fortifier label content suggests
- **Adjustable fortification:** based on serial BUN measurements
  - Assumes that changes in BUN are surrogates for protein intake
- **Targeted, individualized fortification:** based on real-time analysis with human milk analyzers (HMAs)
  - Macronutrient content can be tailored to human milk samples with normal variation
  - Standardizes composition of fortified breast milk to provide consistent and defined macronutrients
  - Used mostly in research setting with little to no cross-over into standard practice due to constraints on time, personnel and resources required

Radmacher PG, Adamkin DH. *Semin Fetal Neonatal Med.* 2017;22(1):30-35.

Calcium and Phosphorus in Human Milk, Term and Preterm Formulas

Fortification of milk and use of preterm formulas help bone mineralization, but both might still need more phosphorous.

	Required per Kg/day	Required per 100 kcal	Human Milk per 100 kcal	Fortified human milk per 100 kcal	Term Formula per 100 kcal	Preterm formula per 100 kcal
Ca, mg	**184**	**170**	45	**156**	75	**170**
P, mg	**126**	**116**	21	**94**	50	**85**

Ca, calcium; P, phosphorus.

1. Motokura K, et al. *JPEN J Parenter Enteral Nutr*. 2020. doi:10.1002/jpen.1993.
2. Ziegler EE. In: Koletzko B et al (eds). *Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines*. Karger; 2014.

Refeeding Syndrome in VLBW/IUGR Infants

- Refeeding Syndrome:
  - Depleted glucose and glycogen stores as a result of undernutrition and starvation
  - Glucose metabolism produces increased phosphate utilization for ATP production
  - Results in fluid and electrolyte dysregulation (hypophosphatemia and hypokalemia)
- In VLBW infants, refeeding syndrome manifests due to:
  - "High-protein" diets leading to depletion of potassium and phosphate as a result of accelerated metabolism
  - Limited fluid, sodium and potassium (and phosphorus) delivery during the first few days of life as clinicians await renal function
  - Resulting electrolyte derangements indicative of ATP depletion, inhibited chemotaxis and phagocyte dysfunction, which increases risk of septicemia

VLBW, very low birth weight; IUGR, intrauterine growth restriction; ATP, adenosine triphosphate.

1. Moltu SJ, et al. *Clin Nutr.* 2013;32(2):207-212.
2. Koletzko B, et al (eds). *Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines*. Karger; 2014.

Key Takeaways

- Nutrition of preterm infants should produce growth rates and body compositions similar to healthy human fetuses of the same GA.
- Nutrition of preterm infants should begin on day 1 and advance from parenteral plus enteral to full enteral nutrition with mother's own milk as soon as possible.
- Enteral feeding of mother's own milk and cumulative intakes of energy and protein are essential for enhancing brain growth and neurocognitive outcomes.
- Fortification of mature mother's own milk and especially donor human milk may be particularly important for the smallest, earliest born preterm infants.