Guidelines for Nutritional Care in the NICU: Author-Led Cases

Pediatric Nutrition
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This activity is supported by an educational grant from
Mead Johnson Nutrition.

Learning Objectives

- Assess updates to the preterm infant nutritional guidelines
- Identify areas of clinical practice impacted by these updates
- Modify clinical practice impacted by these guideline updates in collaboration with members of the preterm infant care team
- Implement preterm nutrition strategies aligned to the updated guidelines

Modules

1. *Nutrition, Growth and Long-Term Outcomes*
   Presented by Tanis R. Fenton, PhD, RD
2. *Preterm Nutrition and the Brain*
   Presented by Sara E. Ramel, MD
3. *Energy Requirements and Carbohydrates in Preterm Infants*
   Presented by Katie A. Huff, MD
4. *Approaches to Growth Faltering*
   Presented by Frank H. Bloomfield, MBChB, MRCP, PhD
5. *Recommended Nutrient Intake Levels for Preterm Infants*
   Presented by Berthold Koletzko, MD, PhD
6. *Human Milk Fortification for Preterm Infants: A Review*
   Presented by Berthold Koletzko, MD, PhD
7. *Preterm Nutrition and Pulmonary Disease*
   Presented by Fernando Moya, MD

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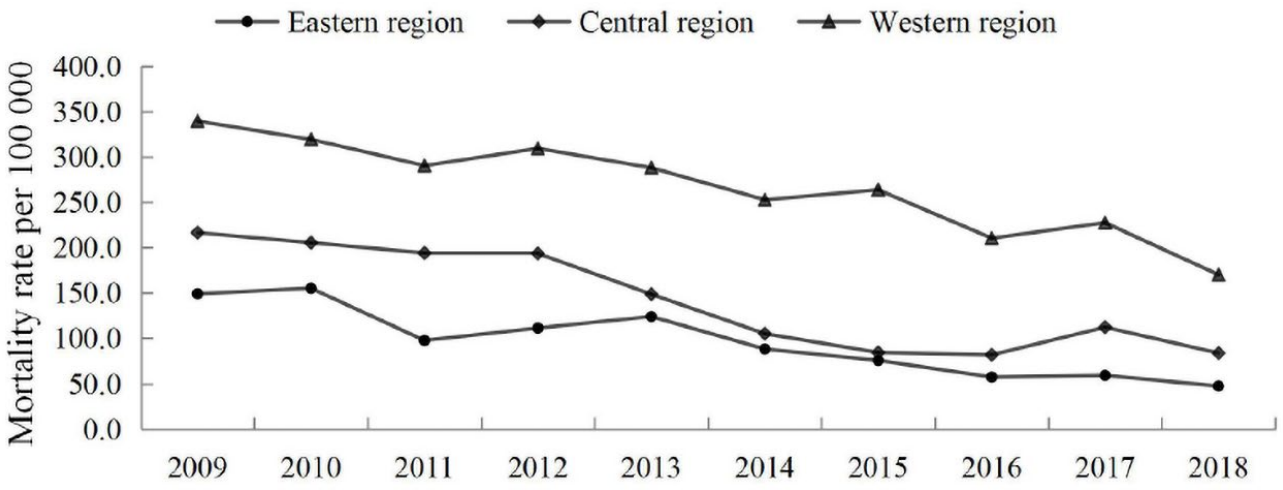
Increased attention to nutritional care of preterm infants

- **Improved survival** of preterms globally *(partic. very/extremely preterms)*

➔ **Long-term outcome** gets greater attention

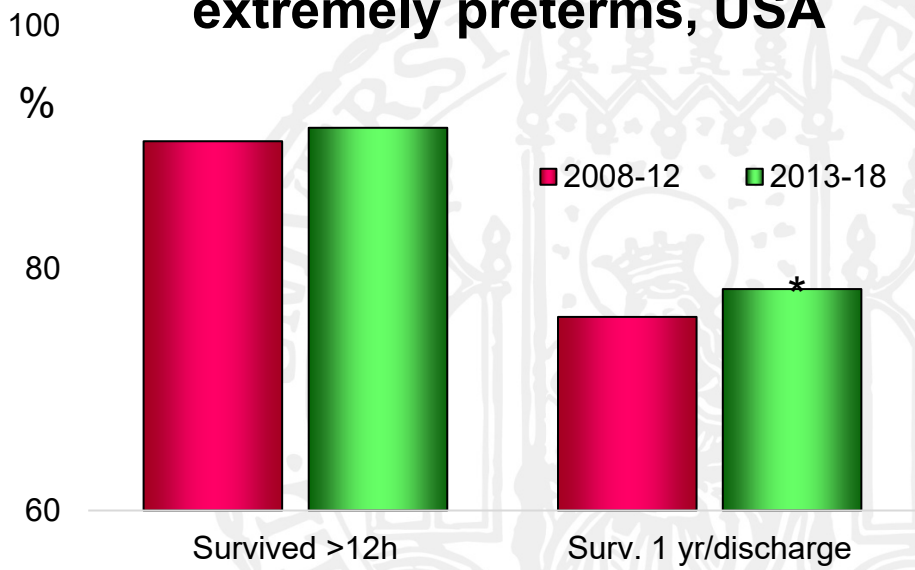
➔ **Greater focus on nutritional care,** *which markedly affects outcome*

Preterm mortality declines, China

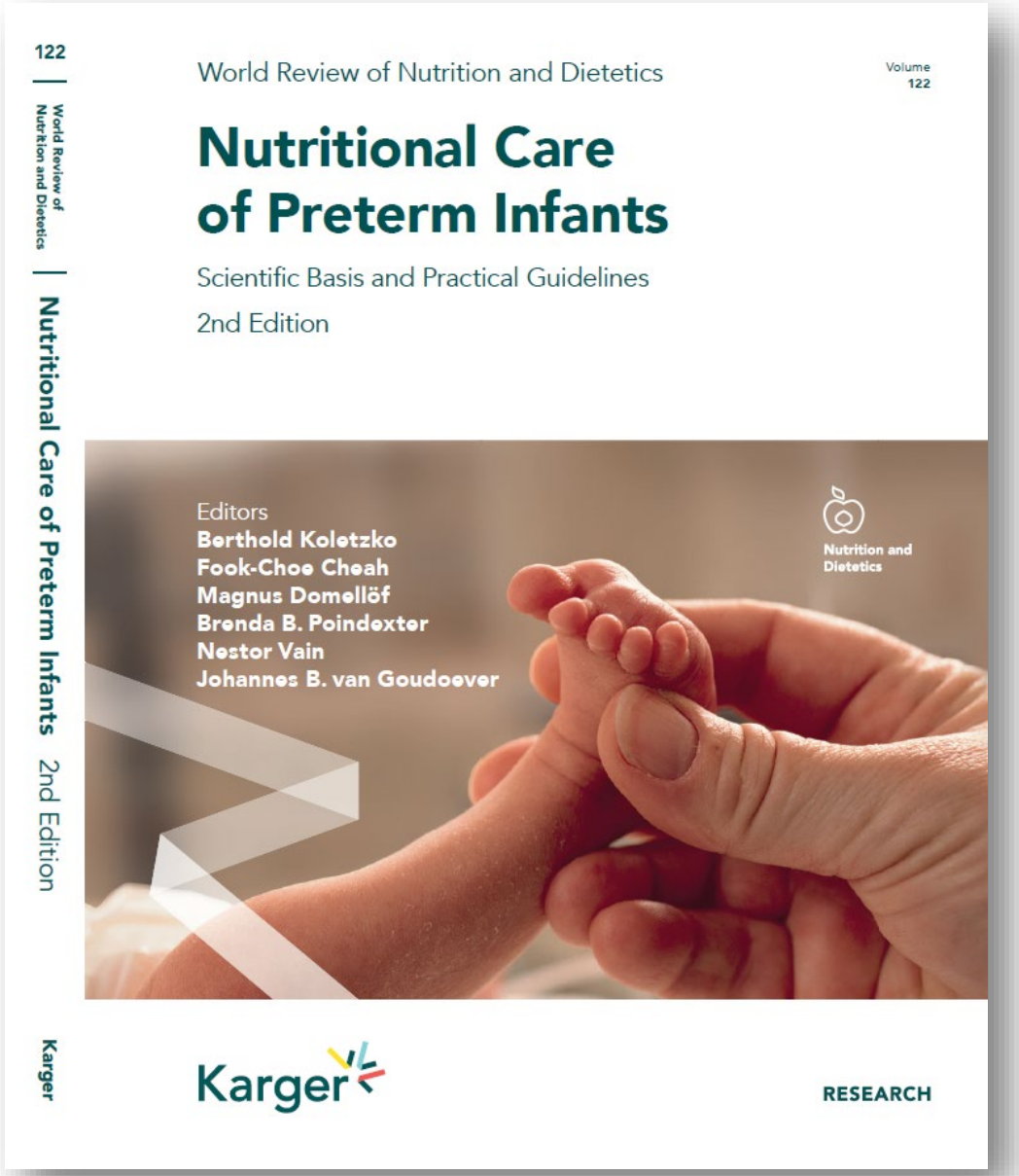


Yu X et al, PLoS One 2021;16(12):e0260611.

Increased survival of extremely preterms, USA



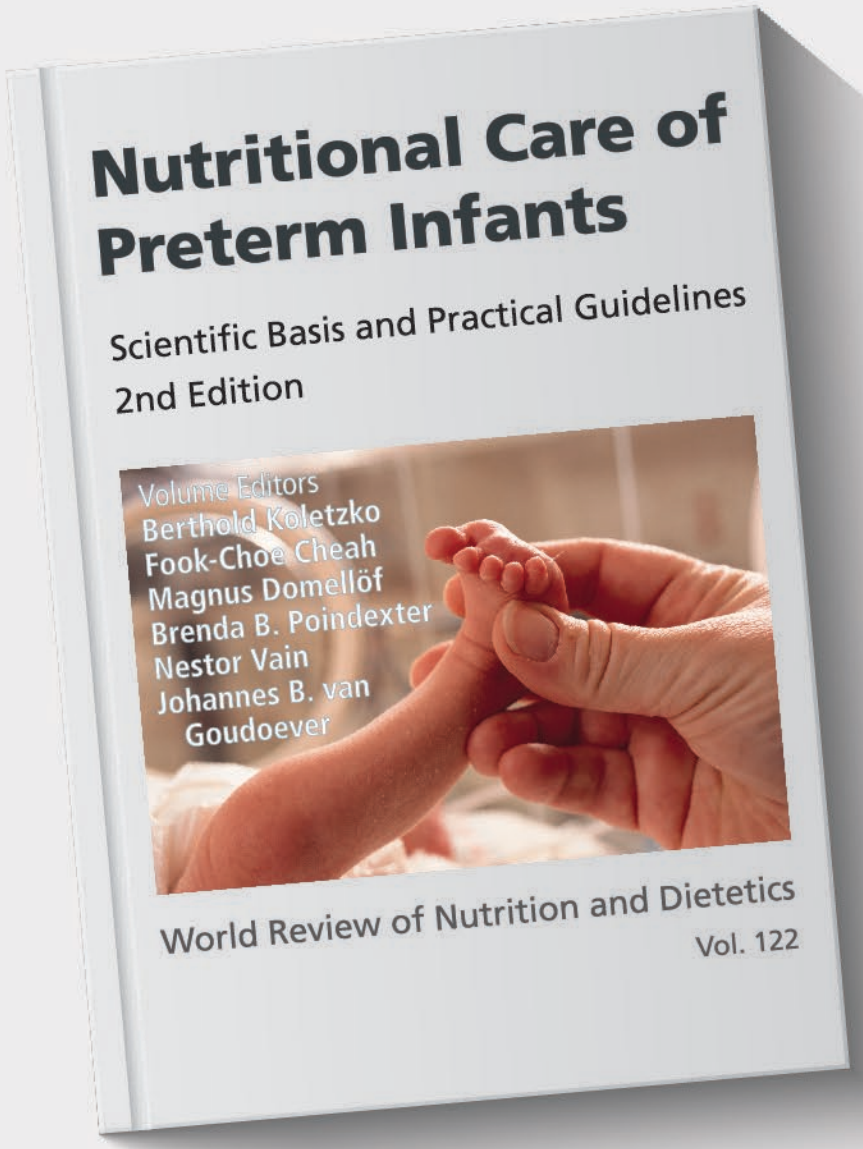
Bell EG et al, JAMA 2022;327(3):248-63.



- Course based on new global recommendations 2021
- Builds on three previous editions *(Tsang et al 1993, Tsang et al 2005, Koletzko et al 2014)*
- Current guidelines developed by leading global experts from the 5 continents
- Recommendations critically peer reviewed *(2 external reviewers + 2 editors)*, carefully revised, and adopted in a formal consensus process *(3 consensus conferences)*

New / revised recommendations, e.g.

- Practice of parenteral nutrition from day 1
- More emphasis of meeting protein needs, early start of amino acids/protein & phosphorus supply
- Early lipid emulsion / higher supply of long-chain PUFA
- Prioritize own mother's milk with fortification
- More attention to feeding after discharge, and more ….



Nutrition, Growth and Long-Term Outcomes

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Faculty Presenter

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Tanis R. Fenton, PhD, RD

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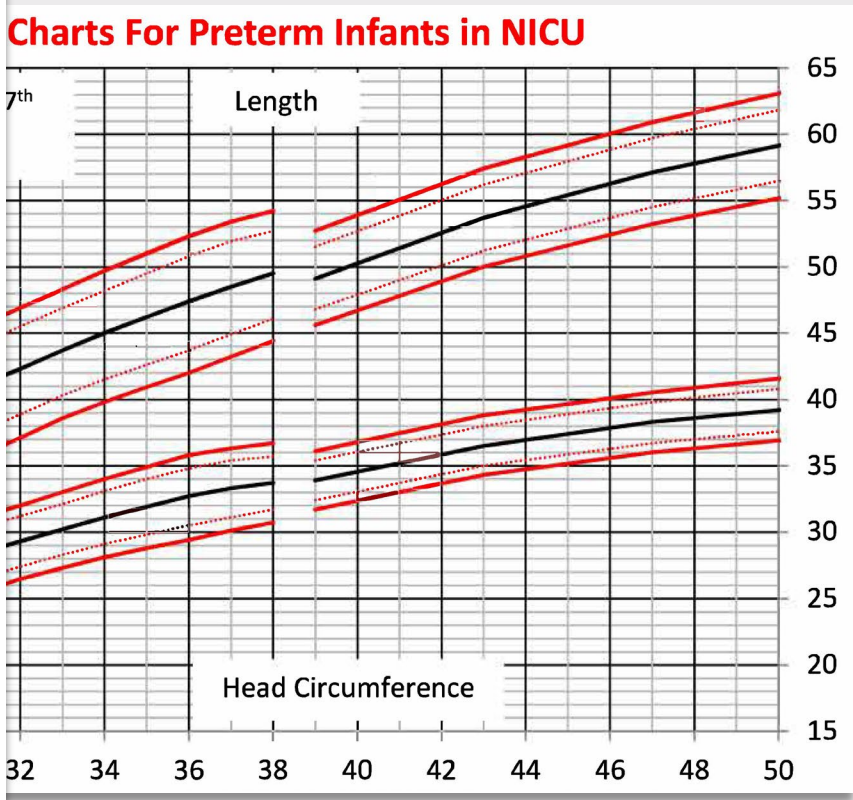
Preterm infants grow very fast	Double or triple birth weight in 2–3 months; twice as fast as term infants
Fetal nutrient accretion	Nutrients to support fetal nutrient accretion to support growth and development
Slow-growth marker	Slow growth is a marker for genetically small or struggling infants due to 1 or more adverse health determinants, morbidities, or NICU stress
Be aware of 1-size-fits-all approach	Preterm infants have unique and various growth potentials

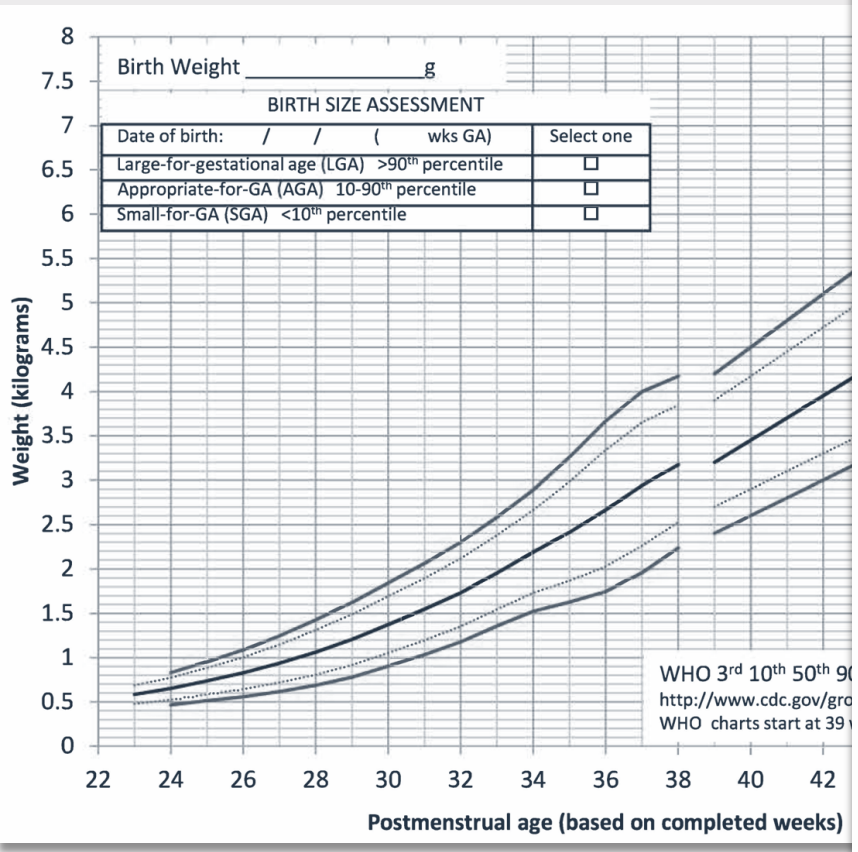
Fenton, TR, Elmrayed, S, Alshaikh, B. Nutrition, growth, and long-term outcomes. In: Koletzko B, et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines.* World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

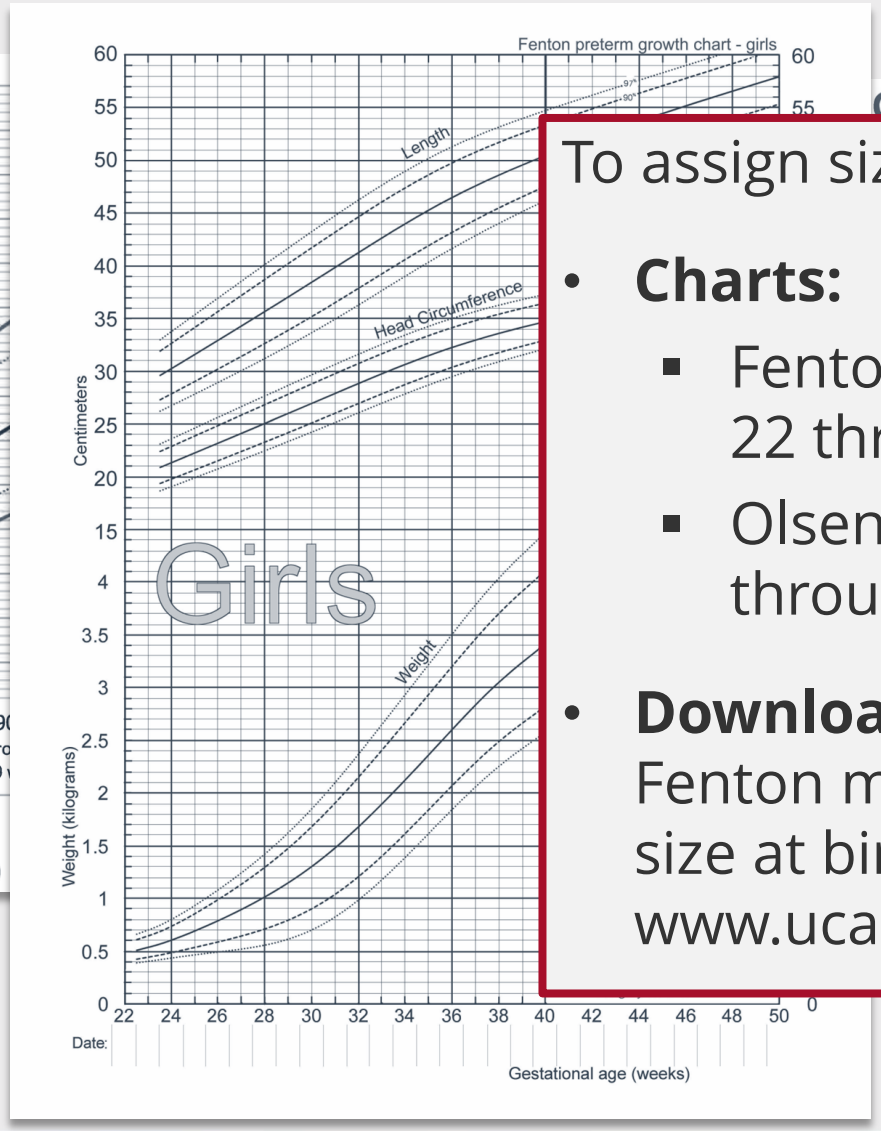
Fenton 2013 & Olsen 2010 Preterm Growth Charts

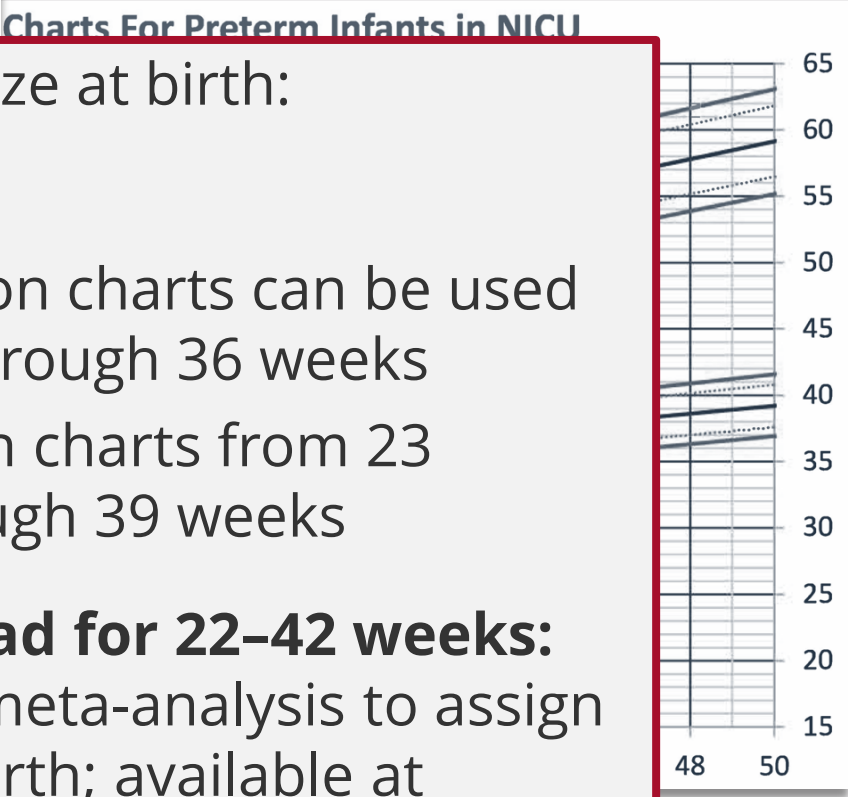


Composite image of preterm growth curves; adapted from Olsen IE, et al. *Pediatrics.* 2010;125:e214–224, and Fenton TR, Kim JH. *BMC Pediatr.* 2013;13:59.

Fenton 2013 & Olsen 2010 Preterm Growth Charts







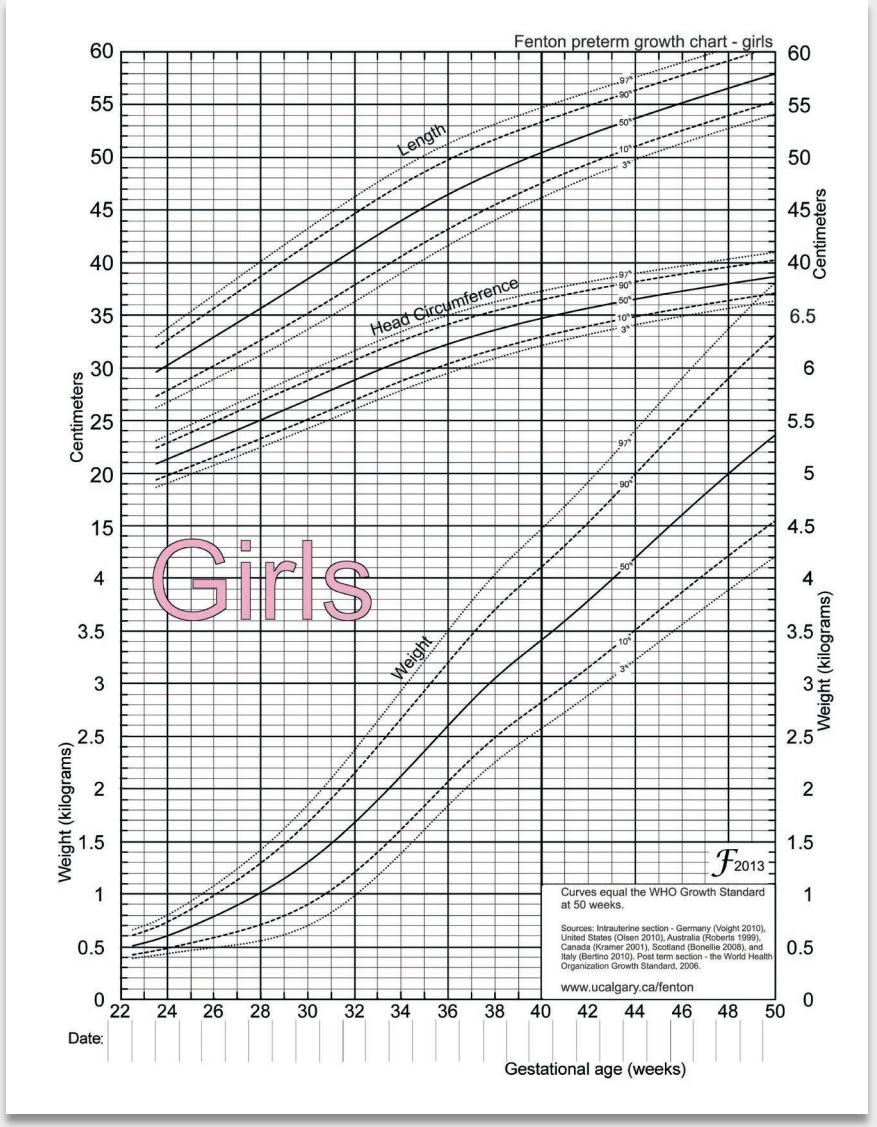
To assign size at birth:

- **Charts:**
  - Fenton charts can be used 22 through 36 weeks
  - Olsen charts from 23 through 39 weeks
- **Download for 22–42 weeks:** Fenton meta-analysis to assign size at birth; available at www.ucalgary.ca/fenton

Composite image of preterm growth curves; adapted from Olsen IE, et al. *Pediatrics.* 2010;125:e214–224, and Fenton TR, Kim JH. *BMC Pediatr.* 2013;13:59.

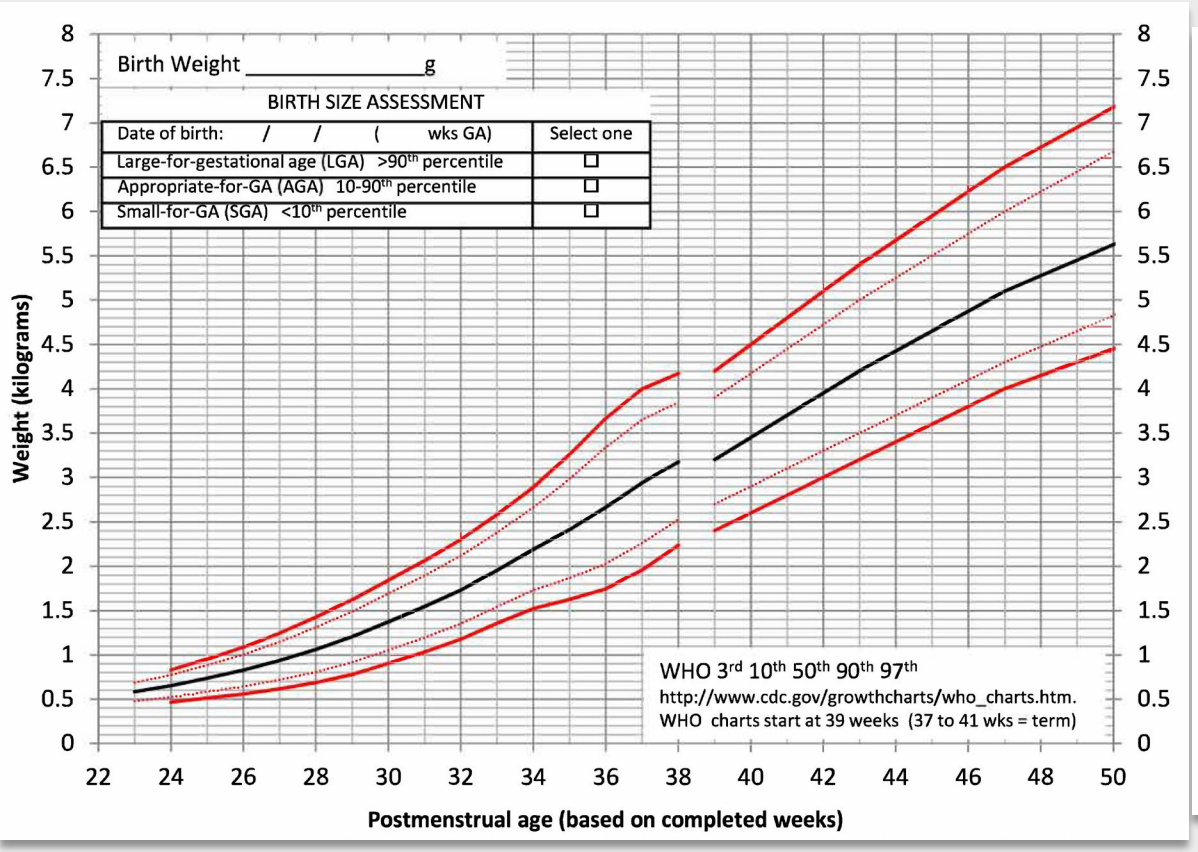
Growth Chart for Preterm Infants

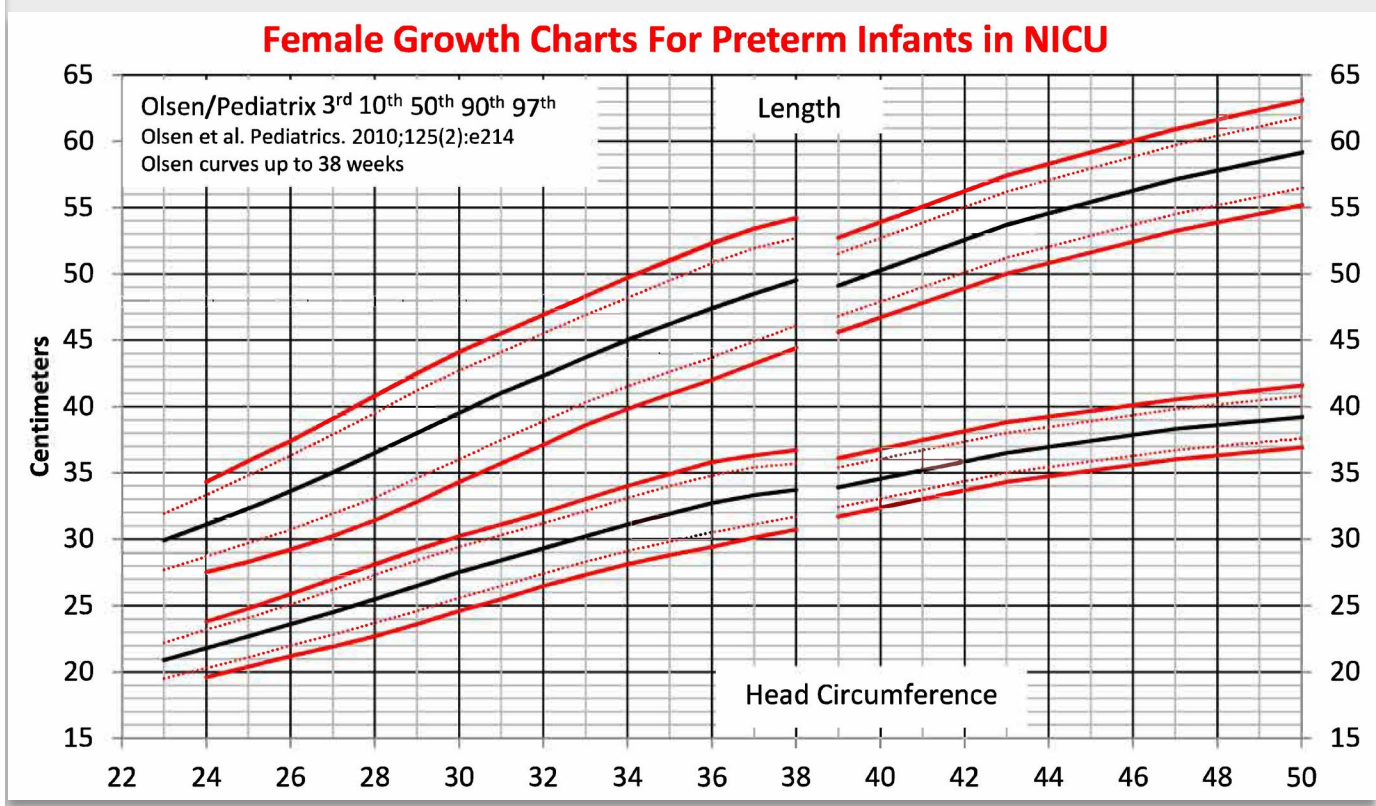
- **Fenton 2013 growth charts** based on 3.9 mm births (includes 34k+ <30 wks) born in Australia, Canada, Germany, Italy, Scotland, and the US between 1991–2007 [1]
- Combined meta-analyses; curves smoothed (based on preterm infant growth patterns) to be equal to the WHO growth standard curves at 10 weeks after term [2]
- **Fenton growth charts**, exact Z-score, and percentile calculators are available at **www.ucalgary.ca/fenton**



1. Fenton TR, Kim JH. *BMC Pediatr.* 2013;13:59. Figure 8 from original; used under terms of a Creative Commons Attribution License.
2. World Health Organization. World Health Organization growth standard. 2020.

Olsen 2010 Preterm Growth Charts





The Olsen charts were developed based on a large American sample of >130k singleton infants born between 1998–2006 and were validated based on a similarly sized sample of infants from the same data set.

Adapted from Olsen IE, et al. *Pediatrics.* 2010;125:e214–224.

Healthcare practitioners concern that preterm infants are at higher risk for obesity, compared to term-born infants, for 2 reasons:

1. Developmental origin of health and disease (DOHaD) hypothesis
2. Higher preterm infant percent body at 40 weeks postmenstrual age

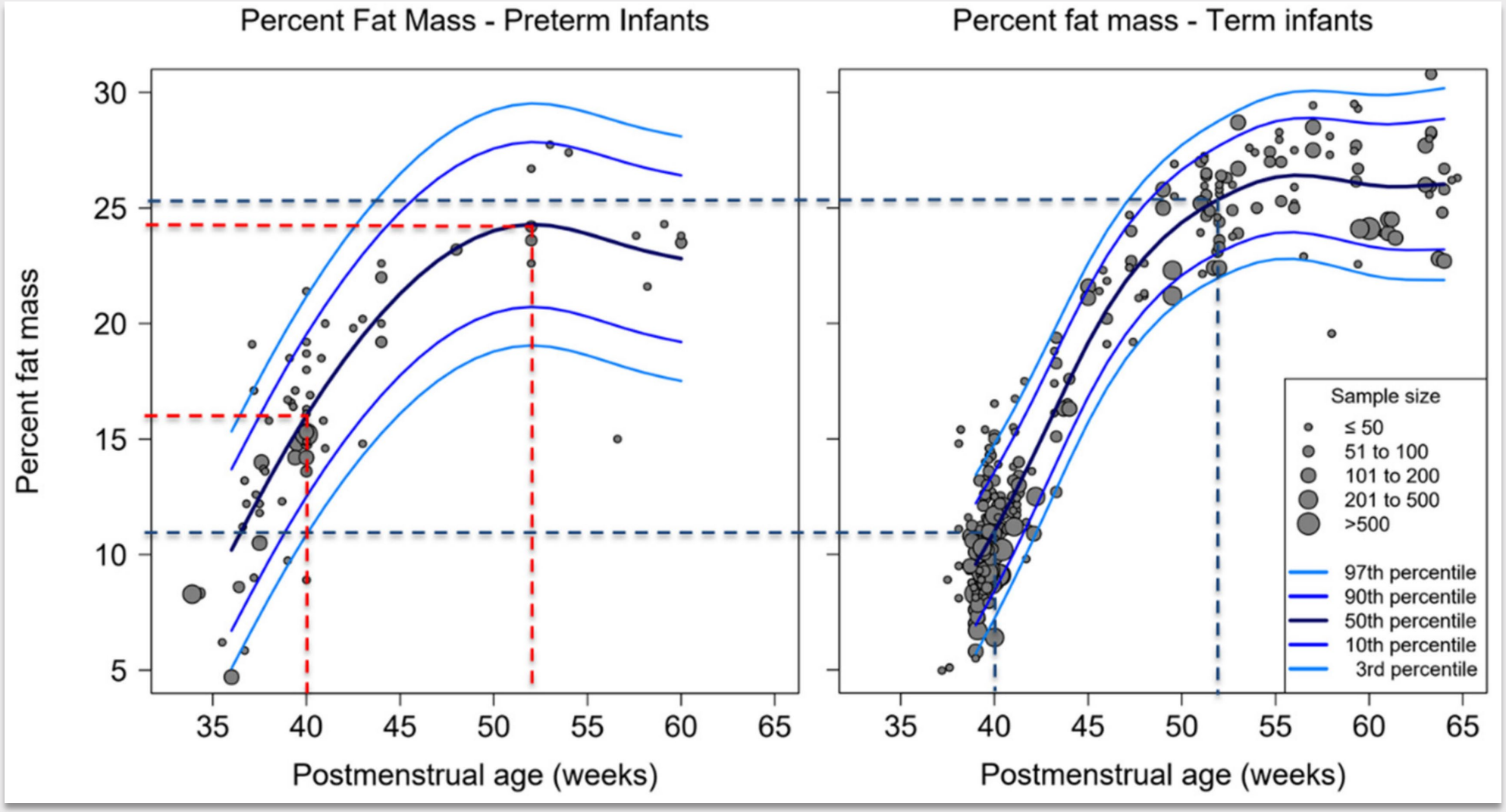
DOHaD, Developmental origin of health and disease.

In contrast to concerns that preterm infants are programmed to be overweight and/or obese later:

- Several studies of preterm infants aged 4–18 years have reported similar weight status [1]–[3] compared to infants born at term.
- While some preterm infants in these studies were overweight, these studies show that, contrary to concerns, preterm infants are **not** at higher risk for overweight than term-born infants.

1. Giannì ML, et al. *Acta Paediatr.* 2015;104:e119– 123.
2. Roberts G, et al. *Pediatrics.* 2013;131:e439–445.
3. Forsum E, et al. *Acta Paediatr.* 2019;108:1704–1708.

Percent fat mass of preterm and term born infants



HOWEVER:

- Preterm-infant percent body-fat differences dissipate as infants grow
- No differences from term-born infants by 3–5 months corrected age

✦ Rather than aiming for a specific weight gain or body composition for preterm infants, a **better goal would be to support preterm infants to grow at rates similar to the fetus.**

Weight below certain percentiles before 40 weeks does not predict low cognitive scores

Study	Small size timing	Development
Hack 1982 [1]	<3rd percentile at 40 weeks	Bayley I scores at 8 months
Tudehope 1983 [2]	<3rd percentile at 40 weeks	Griffith's Developmental Scale scores at 3 years
Shah 2006 [3]	<10th and <3rd percentile at 36 weeks	Bayley II scores at 18–24 months
Zozaya 2018 [4]	<7th percentile at 36 weeks	Bayley II scores at 2 years
Rahman 2020 [5]	<10th percentile at discharge	Bayley III scores at 2 years
Fenton 2021 [6]	Continuous percentiles, 36 weeks	Bayley III at 21 mo & 3 year IQ scores
Salas 2021 [7]	<10th percentile at 36 weeks	Bayley III scores at 2 years

1. Hack M, et al. *Am J Obstet Gynecol.* 1982;143(6):693-699. 2. Tudehope DI, et al. *Aust Paediatr J.* 1983;19(1):3-8. 3. Shah PS, et al. *J Perinatal Med.* 2006;34:484–489. 4. Zozaya C, et al. *Neonatology.* 2018;114:177–180. 5. Rahman A, et al. *Breastfeed Med.* 2020;15(6):362-369. 6. Fenton TR, et al. *World Rev Nutr Diet.* 2021;122:12-31. 6. Salas AA, et al. *Pediatr Res.* 2021;89(7):1804-1809.

What growth of preterm infants matters?

The poor growth that is associated with poor cognitive development:

- The **slowest growing infants**
- Those who are smaller than growth chart curves **after discharge**

What growth of preterm infants matters?

The poor growth that is associated with poor cognitive development:

- The **slowest growing infants**
- Those who are smaller than growth chart curves **after discharge**

✦ *growth rates and longitudinal growth monitoring are better indicators of long-term outcomes than 1-time discharge anthropometric measurements*

Growth Goals for Preterm Infants

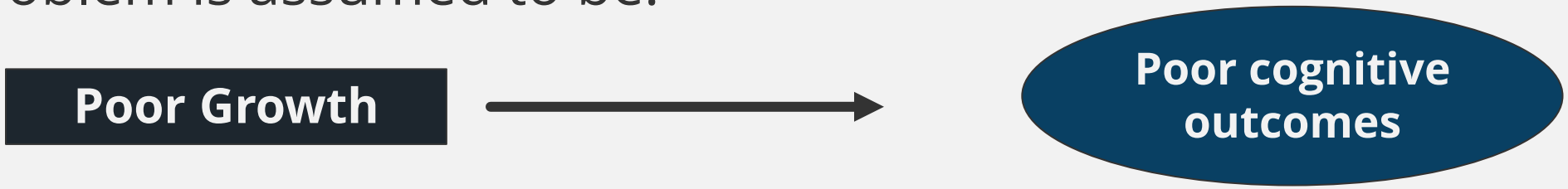
1. Support preterm infants to grow at rates and accrete nutrients similar to the fetus
2. Aim for preterm infant growth to maintain weight, head circumference, and length growth patterns, to aim for growth that is approximately parallel to growth chart curves
3. Increasing weight out of proportion to length does not confer developmental benefits
4. Gaining additional body fat postnatally appears to be a temporary event
5. **If an infant's growth pattern deviates importantly from expected growth patterns, ensure nutrition is optimized and assess for possible contributing factors**
6. Preterm infants are placed lower on growth chart curves after the postnatal weight loss phase.
   ✦**The phrase "extrauterine growth restriction" should be retired and not used to diagnose infants with weight below the 10th or 3rd percentile, because it is not predictive of adverse outcomes.**

These goals were endorsed at the November 5, 2020 Expert Group meeting.

Adapted from Table 1, Fenton, TR, Elmrayed, S, Alshaikh, B. Nutrition, growth, and long-term outcomes. In: Koletzko B, et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

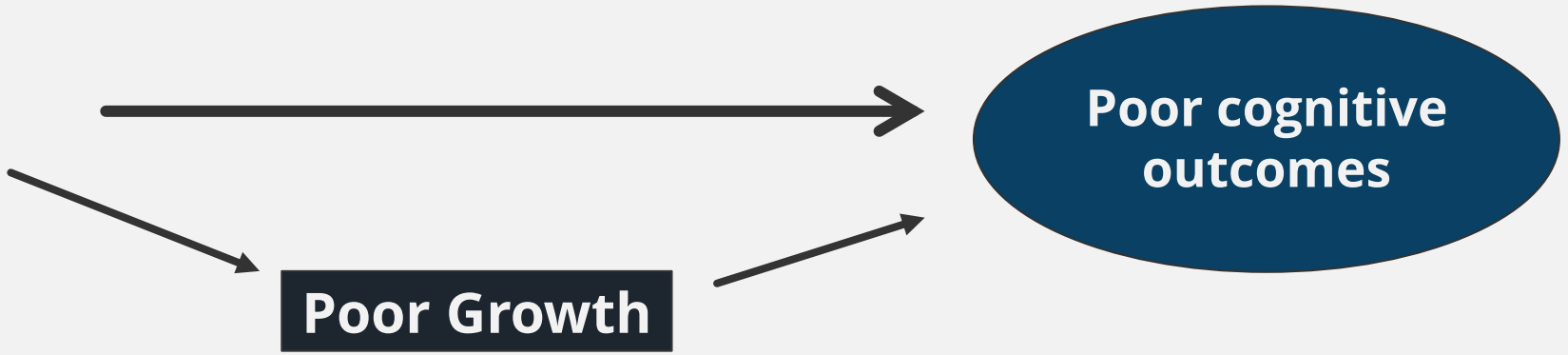
Causal Relationships for Neonatal Outcomes [1],[2]

The problem is assumed to be:



The problem may be:

- Social determinants of health
- Prenatal factors
- Inadequate nutrition
- NICU stress
- Morbidities



Poor growth is more likely an outcome of several possible adverse preterm infants' early life influences and not likely the direct cause of long-term adversity, such as suboptimal development.

1. Adapted from Fig 3, Fenton, TR, Elmrayed, S, Alshaikh, B. Nutrition, growth, and long-term outcomes. In: Koletzko B, et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. World Rev Nutr Diet. Basel, Karger, 2021, vol 122.
2. Bandoli G, et al. *Paediatr Perinat Epidemiol*. 2016;30:521–528

How can the social determinants of health influence preterm infant long-term outcomes?

- As well as neonatal brain injury, **parental education** also predicts cognitive outcomes

- "The association of brain injury with poorer cognition was attenuated in children born to mothers of higher education level, suggesting opportunities to promote optimal outcomes" [1]

✦ Neurodevelopment is modified by families' socioeconomic and education circumstances [1],[2]

1. Benavente-Fernández I, et al *JAMA Netw Open.* 2019;2:e192914.
2. Weisglas-Kuperus N, et al. *Arch Dis Child Fetal Neonatal Ed.* 2008; 94:F196–200.

Meta-analyses: Early macronutrient supplements for preterm infants

- **Improved motor function in toddlers,** especially for girls (13 trials, n = 1406; adjusted mean difference 1.57 [0.14, 2.99]; *P* = 0.03)
- **Did not alter cognitive function** in toddlers (adjusted relative risk [aRR] 0.88 [95% CI 0.68, 1.13]; *P* = 0.31) and older children, although the data were limited for older ages
- **No adverse effects on later metabolic outcomes** (high-density and low-density lipoproteins, cholesterol, fasting glucose, blood pressure, body mass index)

Lin L, Harding JE, et al. *Nutrients.* 2022;14(2):392. doi:10.3390/nu14020392

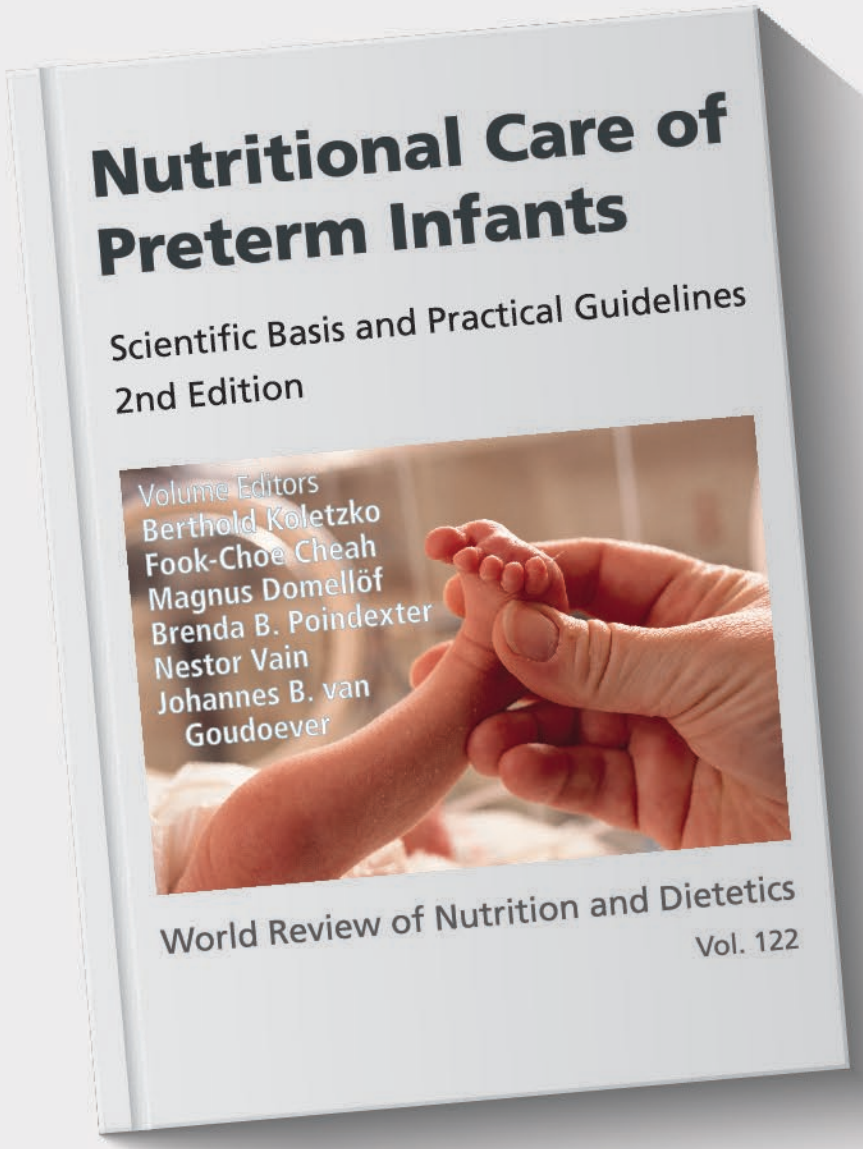
Key Takeaways

- When infants' growth patterns deviate from expected growth patterns, ensure nutrition is optimized. Examine determinants of health and morbidities for possible contributing factors.
- It is important for clinicians to optimize nutrient intakes to meet current recommendations then consider neonatal morbidities as the possible causes for the poor growth velocity.
- Aim for preterm growth to maintain weight, head circumference and length growth patterns. Increasing weight out of proportion to length does not confer benefits.

Research Priorities

- More studies are needed to identify the causes of adverse neurodevelopment to guide interventions and to lessen the burden for infants and their families.

- Long-term follow-up studies, beyond the first few years of life, are needed to explore the effect of different nutrition strategies on neurodevelopment and adult-type disease in children and adults born prematurely.



Preterm Nutrition and the Brain

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Nutrition and the Brain

- All nutrients are important for brain growth and development
- Nutrients that support basic neuronal metabolism and differentiation
  - Proteins, glucose, specific fats
  - Iron, Zinc, Copper, Iodine
- Rapidly developing systems at the time of preterm birth
  - Hippocampus → learning and memory
  - Myelin → speed of processing
  - Cerebellum → balance, motor integration and cognition

Critical Periods for Nutrients
(24- and 44-Weeks Post-Conceptual Age)

- Monitor and optimize overall growth early
- **Starting early matters!**
  - Prompt, adequate nutrient delivery essential to brain health
  - Nutrient delivery must be treated as an emergency to support and optimize neurodevelopmental outcomes
- **Monitor and optimize** vs waiting to manage
  - Nutrient deficits reduce neuron proliferation or differentiation
  - Neuronal trafficking affected by critically timed nutrient deficiency
  - Deficits of protein, energy, iron, zinc, and LC-PUFAs affect neuroanatomy significantly [1],[2]

LC-PUFAs, long-chain polyunsaturated fatty acids

1. Cusick SE, et al. *J Pediatr.* 2016;175:16–21.
2. Fugliestad AJ, et al. In: Nelson CA, Luciana M, eds. *Handbook of Developmental Cognitive Neuroscience*. 2nd ed. MIT Press; 2008. p.623–641.

Macronutrients and Brain Development

- Essential **macronutrients:** protein, fats (eg, LC-PUFAs), glucose [a]
- Carbohydrates, ie, **glucose**, are main fuel source for the brain
  - Preterm infants' glucose infusion rates ~12 mg/kg/min to maintain normoglycemia and growth
- **Fats** necessary for efficient neural processing, >60% of brain's composition
  - Fats (including cholesterol) needed for myelin synthesis, synaptosome formation, and cell membrane fluidity; all crucial for efficient neural processing
  - **LC-PUFAs** supplementation → mature electroretinograms, short-term neurodevelopment gains, improved visual acuity out to 1 year [2]

a. Likely exhibits a critical/sensitive period for neurodevelopment between 24 and 44 weeks after conception based on human data or preclinical models.

1. Georgieff MK, et al. *Dev Psychopathol.* 2015;27:411– 423.
2. Jensen CL, et al. *Clin Perinatol.* 2002; 29:261–281.

Macronutrients—Protein

- **Protein** needed for neurogenesis, dendritic arborization, synaptogenesis, and myelin production
  - Affects cognition
- Infants receiving increased protein in first weeks of life have improved neurodevelopment and brain growth [1]–[3]
  - Every 1 g/kg/d increase in protein during week 1 → 8.2-point increase in MDI on 18-month Bayley [1]
  - 4.5–5 g/kg/day once on enteral feedings is safe and associated with improved linear growth
  - Increased linear growth in first 2 years of life influences cognitive and language development in preterm and term infants [4]–[6]
- Protein accretion is indexed by linear growth and FFM

FFM, fat-free mass.

1. Stephens BE, et al. *Pediatrics.* 2009;123:1337; 2. Isaacs EB, et al. *Pediatr Res*. 2008;63:308–314; 3. Cormack BE, et al. *J Paediatr Child Health*. 2011;47:898–903; 4. Ramel SE, et al. *Neonatology.* 2012;102:19– 24; 5. Belfort MB, et al. *J Pediatr*. 2013;163:1564–9.e1562; 6. Pongcharoen T, et al. *Arch Pediatr Adolesc Med.* 2012;166:411–6.

Micronutrients and Brain Development

- Iron [a], Zinc [a], Copper [a], Iodine [a]
- Monitor micronutrient levels to prevent over- or under-supplementation

Iron assists optimal brain development Exact timing and optimal dosing remain unknown [b]	**Zinc** contributes to neuronal proliferation, differentiation, and myelination [3]–[6]
❑ **Lozoff et al study** revealed lasting cognitive, motor, and social-emotional effects of iron deficiency during infancy [1] ❑ **Steinmacher et al** (n=164) showed infants <1,301 g at birth randomized to early iron suppl. more likely to have a normal neurological exam at 5 yrs [2]	❑ **Firel et al trial** (n=52) formula-fed preterm infants showed improved motor skills at 15 months in group who received higher (2.2 mg/kg/day) vs lower (1.2 mg/kg/day) supplemental zinc dose [7] ❑ **Diaz-Gomez et al** (n=36) showed zinc supplementation at 10 mg/day in NICU reduced linear growth stunting [8]

a. Likely exhibits a critical/sensitive period for neurodevelopment between 24 and 44 weeks after conception, based on human data or preclinical models.
b. Research needed

1. Lozoff B, et al. *Nutr Rev.* 2006;64 Suppl 1:34–43; 2. Steinmacher J, et al. *Pediatrics.* 2007;120:538–546; 3. King JC, et al. *J Nutr.* 2016;146:858S–85S; 4. Frederickson CJ, et al. *Nat Rev Neurol.* 2005;6:449–462; 5. Shu-Zong W, et al. *Development.* 2006;133:3389–3398; 6. Gower-Winter SD, et al. *Biofactors.* 2012;38:186–193; 7. Friel JK, et al. *J Pediatr Gastroenterol Nutr.* 1993;17:97–104; 8. Diaz-Gomez NM, et al. *Pediatrics.* 2003;111:1002–1009.

Nutrition for Improved Growth

Calories and Protein	• Increased calories and protein → improved growth • Increased calories and lipids provided early → improved neurodevelopment
Protein and Energy	• Protein and energy provided in 1st week of life is positively associated with FFM throughout hospitalization
FFM and Weight Gain	• Adequate calories promotes improved growth in weight, length, and FFM gains • Increased FFM and weight gain in NICU in → improved cognitive scores

FFM, fat-free mass.

Ramel SE, et al. *J Pediatr.* 2016;173:108-115. doi:10.1016/j.jpeds.2016.03.003

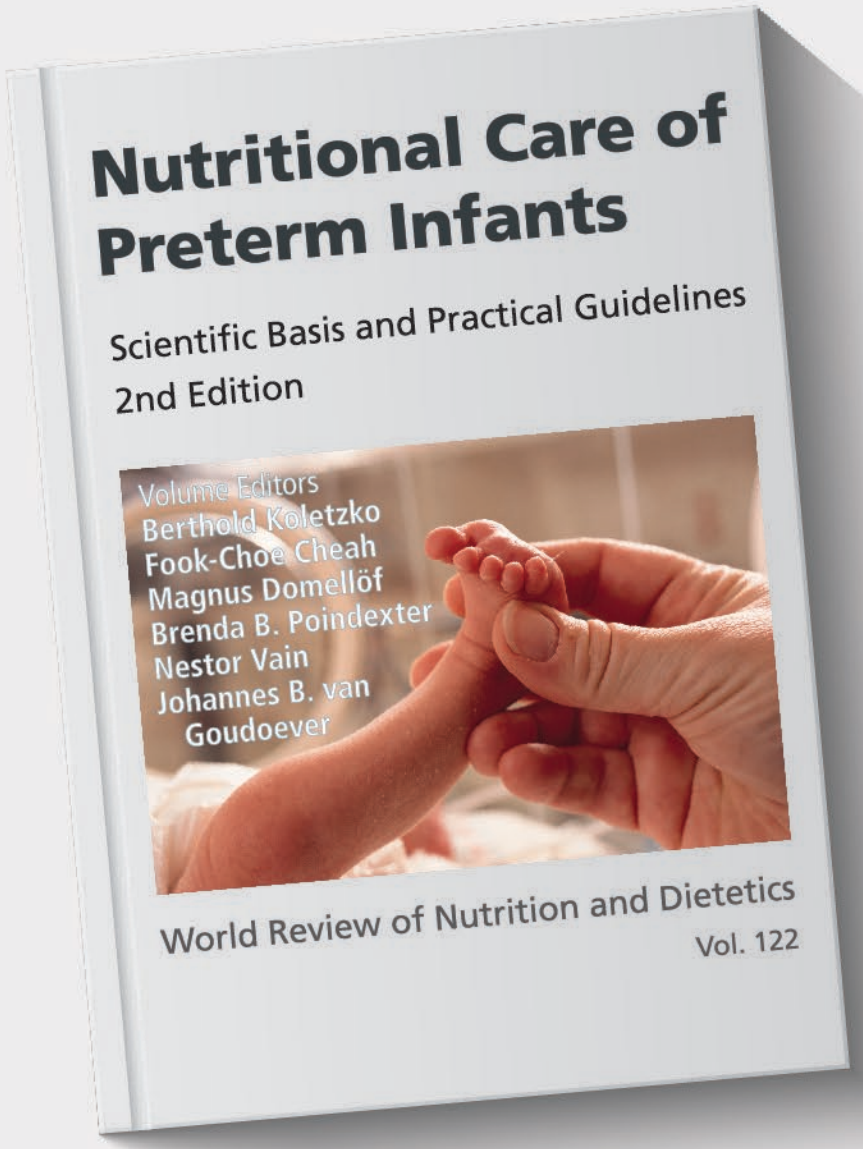
Key Takeaways

- **Routine enteral iron supplementation initiated early in the NICU hospitalization is a safe and effective approach to reducing later neurological and behavioral deficits in preterm infants.**
- **Advance to full enteral feeds of maternal breast milk fortified with the essential nutrients early to ensure optimal growth and neurodevelopmental outcomes.**

Research Priorities

- **Large, randomized, controlled trials of nutrient provision at various dosages and at various times during the NICU stay, are needed to determine the optimal intake of each micro- and macronutrient.**

- **Large, randomized trials are needed to determine the optimal early caloric intake for preterm infants with the goal of optimizing long-term neurodevelopmental outcomes.**



Energy Requirements and Carbohydrates in Preterm Infants

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Katie A. Huff, MD, MS

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Preterm Infants: Balancing Energy and Glucose

Energy requirements	• Influenced by age, weight, and other clinical factors
Energy balance	• Influences weight gain and body composition
Glucose is an important energy source	• Considering preterm infants' large brain and heart to overall weight ratio
Glucose production continues	• Despite glucose supplementation • Excess glucose is related to increased fat deposition and may contribute to hyperglycemia
Balance is essential	• Close monitoring of appropriate glucose supplementation is important • Insufficient and excess total energy intakes should be avoided

Huff KA, et al. Energy requirements and carbohydrates in preterm infants. In: Koletzko B, et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

Energy Intake

Preterm infants require greater energy supply when given enteral vs parenteral supplementation.

Current weight	Parenteral energy [a], kcal/kg/day		Full enteral energy [a], kcal/kg/day
	Starting [b]	Stable patient [c]	
500–1000 g	60–70	100–115 [d]	110–130
1000–1500 g	60–70	90–110	110–130
1500–2000 g	60–70	90–110	110–130
2000–2500 g	45–70	90–110	105–125

a. Calorie intake should be individualized based on patient clinical status and growth. Depending on a patient's energy expenditure, calorie needs may be increased or decreased.
b. Based on IV infusion rates for amino acids of 2.5 g/kg/day, lipids of 2 g/kg/day, and dextrose of 6–8 mg//kg/min starting in the 1st 24 h after birth.
c. These values should be considered minimum values during the transition from parenteral to full enteral nutrition to avoid cumulative deficits in energy and protein if parenteral rates are reduced faster than enteral rates are increased.
d. Based on IV infusion rates for amino acids of 4 g/kg/day, lipids of 4 g/kg/day, and dextrose of 10 mg//kg/min for the most preterm, lowest birth weight infants. Lower amounts of protein are appropriate for more mature infants.

Huff KA, et al. Energy requirements and carbohydrates in preterm infants. In: Koletzko B, et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. World Rev Nutr Diet. Basel, Karger, 2021, vol 122. Table adapted from Table 1. Adapted from original data DeMarie MP, et al. *J Perinatal Med*. 1999;27(6):465–472; Agostoni C, et al. *J Affect Disord*. 2017; 224:10–15. Kashyap S, et al. In: Thureen PJ, et al, eds. *Neonatal Nutrition and Metabolism*. 2nd ed. Cambridge University Press; 2006:134–146; Ziegler EE. Nestle Nutr Workshop Ser Pediatr Program. 2007;59:161–172; Joosten K, et al. *Clin Nutr*. 2018;37:2309–2314; Nutritional needs of the preterm infant. In: Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 8th ed. AAP; 2019:113–62; Agostoni C, et al. *J Pediatr Gastroenterol Nutr*. 2010;50:85–91.

Energy: Recommended Dosing Requirements

- Energy requirements vary based on multiple patient, environmental, and clinical factors
- Consider these factors on an individual basis when determining energy needs of a patient:
  - 110 kcal/kg/day should ensure adequate energy for brain growth and to prevent retinopathy of prematurity [1]
  - 130 kcal/kg/day may be needed in infants who experience growth faltering
- Energy expenditure in preterm infants varies widely (40–76 kcal/kg/day) [2]–[4]

1. Stoltz Sjostrom E, et al. *Arch Dis Child Fetal Neonatal Ed*. 2016;101:F108–113.
2. Kashyap S, et al. Energy requirements and protein-energy metabolism and balance in preterm and term infants. In: Thureen PJ, et al, eds. *Neonatal Nutrition and Metabolism*. 2nd ed. Cambridge University Press; 2006:134–146.
3. DeMarie MP, et al. *J Perinatal Med.* 1999;27(6):465–472.
4. Leitch CA, et al. Energy. In: Tsang RC, et al, eds. *Nutrition of the Preterm Infant*. 2nd ed. Digital Educational Publishing; 2005: 23–44.

Physiological factors influencing energy expenditure and energy requirement in the preterm infant

Physiological factor	Effect on energy requirement
Age	EE increased with increasing chronological age
Physical activity	• Accounts for 3%–17% of EE, but lower values most of the time • Lower physical activity noted with lower gestational age and with swaddling
Dietary intake	• Increased EE via digestion, absorption, nutrient transport across membrane, mechanical activity, metabolism, and storage • Diet-induced thermogenesis increases EE by 10%–15% • Increased EE with formula feeding vs breast milk feeding
Environmental interactions	• Hot and cold environments increase EE • Positioning of infant affects EE with prone lowering EE by 10% compared to supine • Stress induced by interaction with environment increases EE in preterm infant
Clinical conditions	• EE increases during sepsis (estimates 20%–50%) • Increased respiratory demands, including chronic lung disease associated with increased EE
Medications	• Caffeine increases EE • Dexamethasone has no effect on EE or energy balance but decreases weight gain, altering tissue accretion

EE, energy expenditure.

Huff KA, et al. Energy requirements and carbohydrates in preterm infants. In: Koletzko B, et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. World Rev Nutr Diet. Karger, 2021, vol 122. Table adapted from Table 2, and from Hay WW Jr, et al. In: Koletzko B, et al. eds. *Nutritional Care of Premature Infants*. World Rev Nutr Diet. Karger; 2014;110:64–81; Towers HM, et al. *Pediatr Res.* 1997;41:584–589; Bell EF, et al. *Am J Perinatol.* 2017;34:493–498; Lin HC, et al. *J Spec Pediatr Nurs.* 2014;19:331–338.

Carbohydrates and the Preterm Infant

- Glucose is the main energy source for the brain and heart.
  - Neonate has same glucose demands as a fetus of the same gestational age.
- A normal glucose utilization rate in preterm infants is 6–8 mg/kg/min.[1],[2]
- Maximal glucose utilization rates are about 11–13 mg/kg/min.[1]
- Extremely preterm infants continue glucose production at 2–3 mg/kg/min despite adequate supplementation.[3]

1. Hay WW Jr. *Pediatr Gastroenterol Hepatol Nutr.* 2018; 21: 234-247.
2. Mesotten D, et al. *Clin Nutr.* 2018; 37:2337-2343.
3. Chako SK, et al. *J Pediatr.* 2011; 158:891-896.

Glucose Infusion Requirements

Current weight	Starting parenteral glucose [a]		Full parenteral glucose [a]		Full enteral carbohydrate, g/kg/day
	g/kg/day	GIR, mg/kg/min	g/kg/day	GIR, mg/kg/min	
500–1000 g	4–12	3–6 [a]	10–15	7–10 [b]	11–13 [c]
1000–1500 g	6–12	4–8	10–15	7–10	11–13
1500–2000 g	6–12	4–8	10–15	7–10	11–13
2000–2500 g	6–12	4–8	10–15	7–10	11–13

a. GIRs should be increased or decreased in response to frequent plasma glucose concentration measurements to maintain normoglycemia.
b. Higher values up to 9–12 mg/min/kg might be needed based on larger brain/body weight ratio in very preterm and asymmetric SGA infants and IUGR/SGA infants with hyperinsulinism-like disorders.
c. Based on a feeding rate of 160 mL/kg/day.

GIR, glucose infusion rate; SGA, small for gestational age; IUGR, intrauterine growth restriction.

Huff KA, et al. Energy requirements and carbohydrates in preterm infants. In: Koletzko B, et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. World Rev Nutr Diet. Basel, Karger, 2021, vol 122. Table adapted from Table 3, and from Nutritional needs of the preterm infant. In: Kleinman RE, Greer FR, eds. *Pediatric Nutritio*n. 8th ed. AAP; 2019:113–62; Mesotten D, et al. *Clin Nutr.* 2018;37:2337–2343; Agostoni C, et al. *J Pediatr Gastroenterol Nutr.* 2010;50:85–91.

Key Takeaways

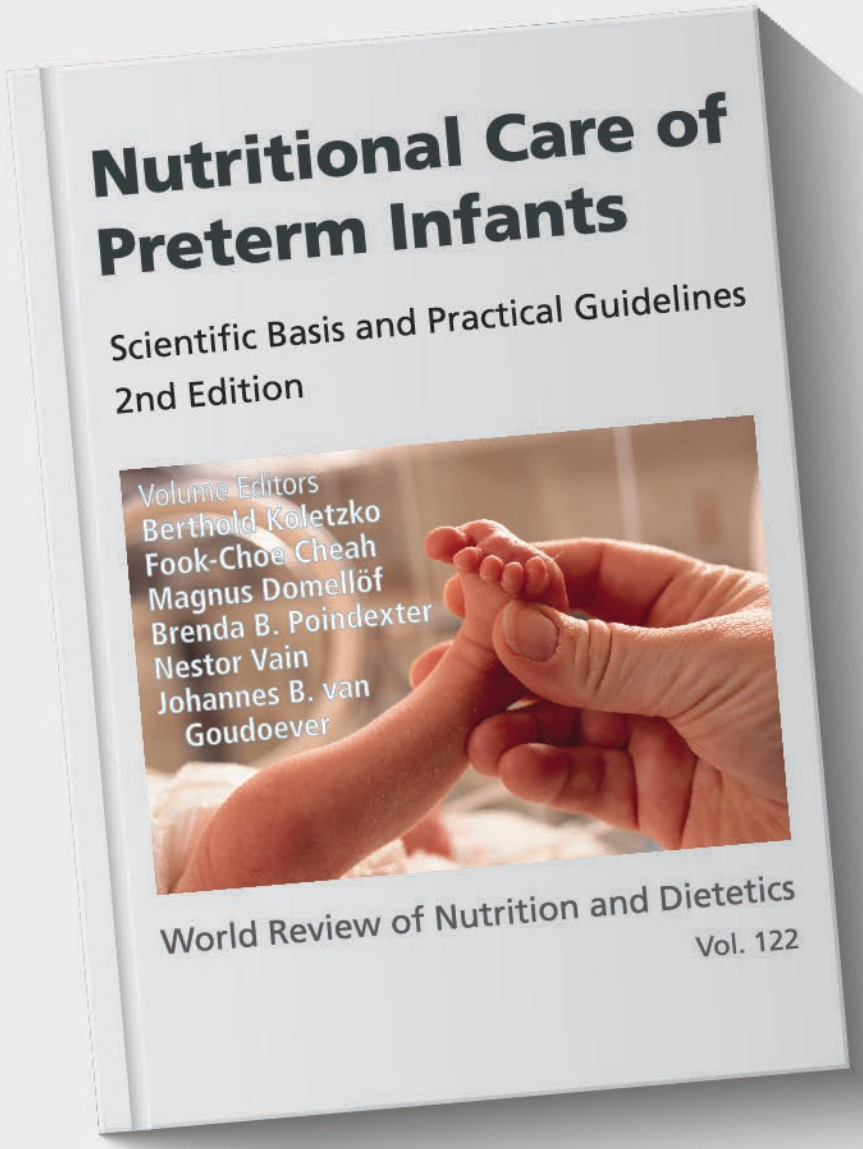
- **Energy needs are influenced by gestational and postnatal age, as well as environmental and clinical factors (eg, need for catch-up growth, lung disease), so adjust per individual preterm infant needs.**

- **Glucose is an important energy source, but excess can lead to adverse effects of hyperglycemia.**

Research Priorities

- Research is needed to determine the ideal ratio of protein, glucose, and fat intake for improved lean body mass accumulation in preterm infants to emulate the body composition of the fetus more closely at the same gestational age.

- Research is needed in preterm patients to apply the data from continuous subcutaneous glucose monitoring to prevent hypo- and hyperglycemia.



Approaches to Growth Faltering

Brenda B. Poindexter
Barbara E. Cormack
Frank H. Bloomfield

Faculty Presenter

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Frank H. Bloomfield, MBChB, MRCP (UK)**, PhD**

No relationships to disclose

The grantor, Mead Johnson Nutrition, had no involvement in selecting faculty, editorial decisions, content or writing of this educational material.

What Is Faltering Growth in a Preterm Baby?

- Faltering growth is dynamic and not defined by a given centile on a growth chart at a single point in time
- Contraction of extracellular fluid (ECF) after birth results in a fall in weight centile for all preterm babies
  - On average, this is approximately 0.8 Z-score
- Faltering growth is a fall across centiles after this ECF contraction
  - A baby growing along a centile below the 10th may have perfectly adequate growth

Faltering Growth Is Common in Very Preterm and Very Low-Birth-Weight Babies

- As a population, preterm babies are smaller than gestational-age-matched fetuses who go on to a term birth
- Fetal nutrient requirements are high to support rapid growth
  - Matching these levels after birth is challenging
- Weight is a measure of mass, not of growth
  - Declines in length and head circumference often exceed those of weight

1. Higgins RD, et al. *J Pediatr.* 2012;160:511–516.
2. Rochow N, et al. *Pediatr Res.* 2016;79:870–879
3. Landau-Crangle E, et al. *JPEN J Parenter Enteral Nutr.* 2018;42:1084–1092.

Nutrient Requirements for Very Preterm Babies

Fetal protein uptakes	• ~ 3.5 g/kg/day amino acids via placenta • ~ 0.5 g/kg/day of enteral protein from swallowed amniotic fluid = minimum of 4 g/kg/day of protein
Low birth weight infant	• Glucose stores ~200 kcal at birth • Obligatory turnover 1%–2% body protein/day ▪ minimum of 1.5 g/kg/day protein required to avoid nitrogen deficit
Protein requirements for ELBW in the first week	• Minimum 2 g/kg/day protein & 2 g/kg/day of lipid in the first 24 h after birth • 3.5–4.0 g/kg/day protein & 34 g/kg/day of lipid by day 3 • 120 kcal/kg/day & 3.8 g/kg/day of protein intake thereafter

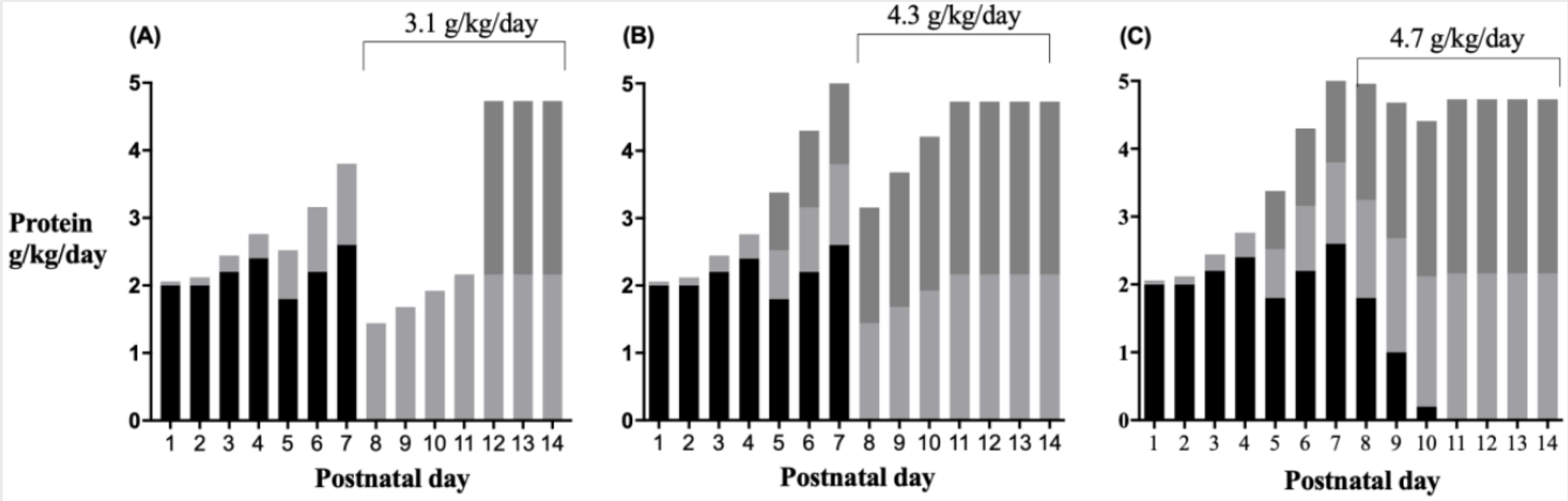
✦ **Close attention to nutritional intakes is essential as actual intakes often fall behind prescribed intakes**

1. Hertz D, et al. *J Clin Invest.* 1993;92:1752–8. 2. Mulvihill SJ, et al. *J Pediatr Surg.* 1985;20:668–672. 3. Embleton ND, et al. In: Koletzko B, Poindexter B, Uauy R, eds. *Nutritional Care of Preterm Infants*. World Rev Nutr Diet. Karger; 2014:177–189.
4. Senterre T, et al. *J Pediatr Gastroenterol Nutr.* 2011;53:536–542.

Risk Factors for Faltering Growth

- Nutrient intakes often fall behind intended/prescribed intakes
  - eg, other infusions / antibiotics
- Concern re elevated serum urea concentrations
- Increased energy requirements
  - Bronchopulmonary dysplasia, congenital heart disease
- Micronutrient depletion (eg, sodium, zinc)
- Malabsorption (eg, high output stoma)
- Be cognizant of the transition from intravenous to enteral nutrition

Transition to Enteral Feeds



Enteral feed volume at which PN discontinued: (A) and (B) 120 mL/kg/d; (C) 180 mL/kg/d

Enteral feed volume at which breastmilk fortifier added: (A) 180 mL/kg/d; (B) and (C) 5 mL every 2 hours

Higgins RD, et al. *J Pediatr.* 2012;160:511–516. Rochow N, et al. *Pediatr Res.* 2016;79:870–879. Koletzko B, et al. eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. World Rev Nutr Diet. Basel, Karger, 2021, vol 122. Figure 1 from original.

Human Milk Fortification

- The high nutritional requirements of preterm babies mean human milk given in "usual" volumes may not provide adequate nutrition
  - Increased volumes (eg, ≥ 200 mL/kg/d) or addition of a multicomponent milk fortifier may be required
- Human milk fortifiers lead to short-term improvements in growth [1]
  - Evidence for long-term benefit on neurodevelopment is lacking
- Donor human milk has significantly lower nutritional value than mother's own milk
  - Infants receiving donor human milk likely require nutritional supplements

1. Amissah EA, et al. *Cochrane Database Syst Rev.* 2018;6:CD000433.

Monitoring Growth Faltering

- Identify and address growth faltering as early as possible through routine monitoring and evaluation of growth trajectory
  - Length and head circumference are just as important, and a better measure of quality of growth, than weight
- Weight, length, and head circumference must be measured accurately using standard techniques with appropriate equipment
  - Head circumference (weekly): use nonstretch measuring tape
  - Length (weekly): use a neonatometer or length board (readily available for use inside incubators)
  - Weight (2 or 3 times a week)
- Converting measurements to Z-scores allows simple evaluation of Z-score change
  - Controls for sex and gestational age

Causes of Growth Faltering

Nutrient/indicator	Potential cause of faltering growth if:
Fluid restriction	< 160–180 mL/kg/day High stoma output (consider replacing stoma output into distal mucous fistula)
Protein inadequate	Blood urea nitrogen < 1.6 mmol/L (4.48 mg/dL)
Energy inadequate	< 110–130 kcal/kg/day (enteral)
Sodium depletion (whole body)	Urine Na < 20 mmol/L especially if high stoma output
Zinc	Serum zinc < 10 µmol/L
Fat malabsorption	Steatocrit > 10%–20% (often higher in neonates) Fecal chymotrypsin < 13 U/g
Carbohydrate malabsorption	Reducing substances • trace (+) – ignore • small (++) – repeat • moderate/large (> ++) – consider lactose-free feed Stool pH > 6.0 indicates secretory diarrhea
Gastroesophageal reflux	There is no indication to measure gastric residuals
Increased energy requirement	Congenital heart disease (especially with left-to-right shunt) Increased work of breathing

Koletzko B, et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. World Rev Nutr Diet. Basel, Karger, 2021, vol 122. Adapted from Table 3.

Intervention Strategies

Options to increase enteral energy and macronutrient intakes:

- Increase enteral volume (eg, ≥ 200 mL/kg/d human milk)
- Human-milk-derived fortifiers (if available / affordable)
- Multicomponent bovine-derived fortifiers
- Protein as liquid protein concentrate / whey protein / amino acid powder
- Increase lipid emulsion intake
- Enteral fat emulsion: long-chain or medium-chain triglyceride
- Carbohydrate as glucose polymers
- Formula powder/concentrate formula if not fed human milk

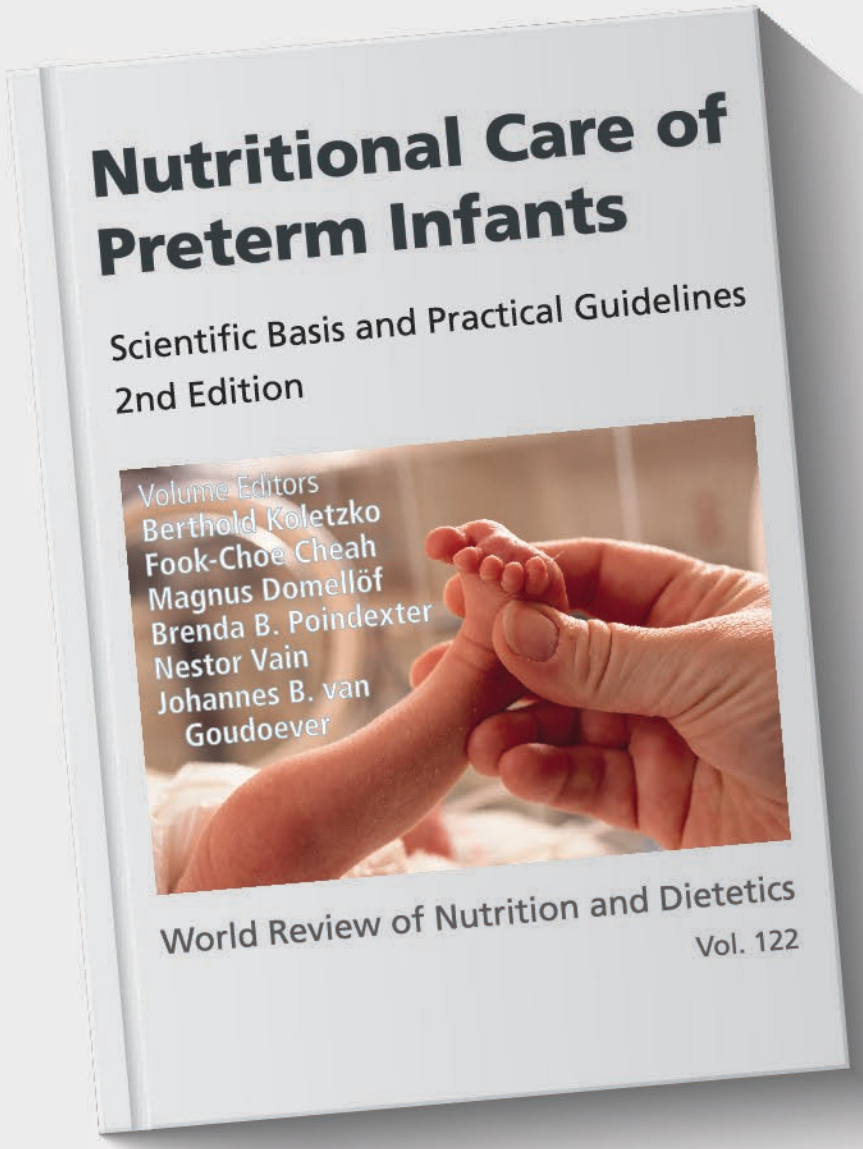
American Academy of Pediatrics Committee on Nutrition. Nutritional needs of the preterm infant. In: Kleinman R, Greer F, eds. *Pediatric Nutrition.* 8th ed. Itasca: American Academy of Pediatrics; 2019:113.

Key Takeaways

- All 3 growth parameters—weight, length, head circumference—should be monitored on a standardized growth chart.
- Observe growth trajectory, including length, not just the position on a centile chart at a given point in time.
- Prevention of growth faltering is the ideal, but when growth faltering does occur, prompt recognition, identification of contributing factors and appropriate intervention are necessary.

Research Priorities

- Determination of the growth trajectory required to support optimal neurodevelopment.
- Large trials needed to determine if fortification of human milk improves long-term outcomes without short-term cost.



Recommended Nutrient Intake Levels for Preterm Infants

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Faculty Disclosures

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Berthold Koletzko, MD, PhD

Berthold Koletzko tends to be biased towards breastfeeding as member of the German National Breastfeeding Committee, Chair Nutrition Committee, German Paediatric Society, and Past-President, Int Soc Research on Human Milk & Lactation. LMU - Ludwig Maximilians Universität Munich and its employee BK received support for scientific and educational activities from the European Union (EU) Programmes DYNAHEALTH-633595, Lifecycle-733206 and CoreMD 965246, EU Research Council Advanced Grant META-GROWTH ERC-2012-AdG–no.322605, EU Erasmus+ Early Nutrition eAcademy Southeast Asia-573651-EPP-1-2016-1-DE-EPPKA2-CBHE-JP and Capacity Building to Improve Early Nutrition and Health in South Africa-598488-EPP-1-2018-1-DE-EPPKA2-CBHE-JP, EU Interreg Focus in CD-CE111, EU Danube CD-Skills DTP3-572-1.2, EU Joint Programming Initiative HDL projects NutriPROGRAM, EndObesity and BiomarKids, German Ministry of Education and Research 01EA1904 and 01 EA 2101, German Ministry of Health 1503-68403-2021, German Research Council Ko912/12-1 and INST 409/224-1 FUGG, Alexander von Humboldt Foundation 3.3 - 1218469 - POL - HFST-E, US National Institutes of Health 1R03HD087606-01A1, Else Kröner Fresenius Foundation, Family Larsson Rosenquist Foundation, and healthcare and nutrition companies i.e. Bayer, Barilla, Danone, DGC, DSM, Hipp, Nestlé and Reckitt. BK is the Else Kröner Seniorprofessor of Paediatrics at LMU University of Munich, financially supported by Else Kröner-Fresenius-Foundation, LMU Medical Faculty and LMU University Hospitals.

The grantor, Mead Johnson Nutrition, had no involvement in selecting faculty, editorial decisions, content or writing of this educational material.

Defining reference nutrient intakes

- Goal: meet physiological requirements to maintain normal growth & health
- Review of scientific evidence/literature: for several nutrients lack of conclusive studies ⇨ considerable uncertainties on adequate intakes
- For several nutrients, needs are related to weight gain velocity

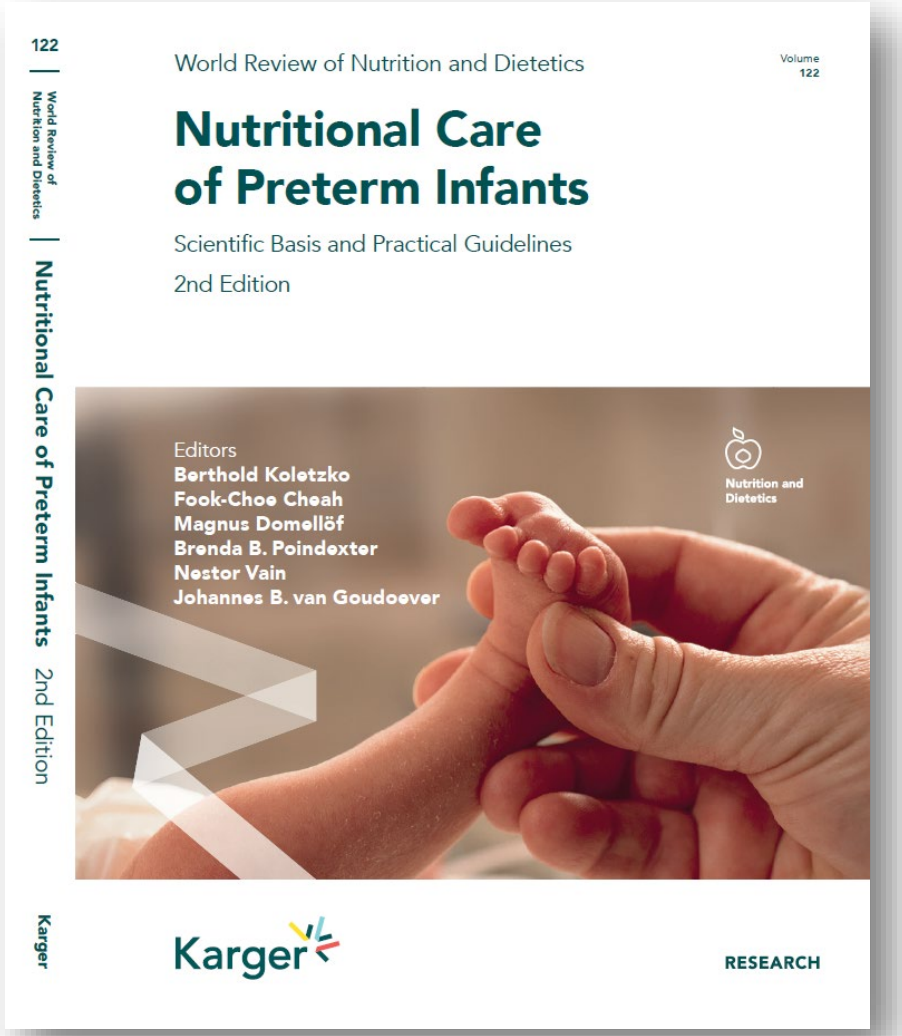
⇨ Daily intakes per kg/body weight

⇨ Nutrient levels per 100 kcal intake based on energy supply of 110 kcal/kg&d

Body weight	Desired weight gain (g/kg &d)
< 1500 g	17-21
1500-2000 g	14-17
2000-2500 g	12-14
2500-3000 g	10-13

Koletzko B et al, Defining nutritional needs of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants, Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Defining reference nutrient intakes



Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

- Leading experts reviewed evidence and drafted text and recommendations
- Critical peer review *(2 external reviewers + 2 editors)* & careful revision
- Formal consensus process *(3 consensus conferences with authors and editors)*

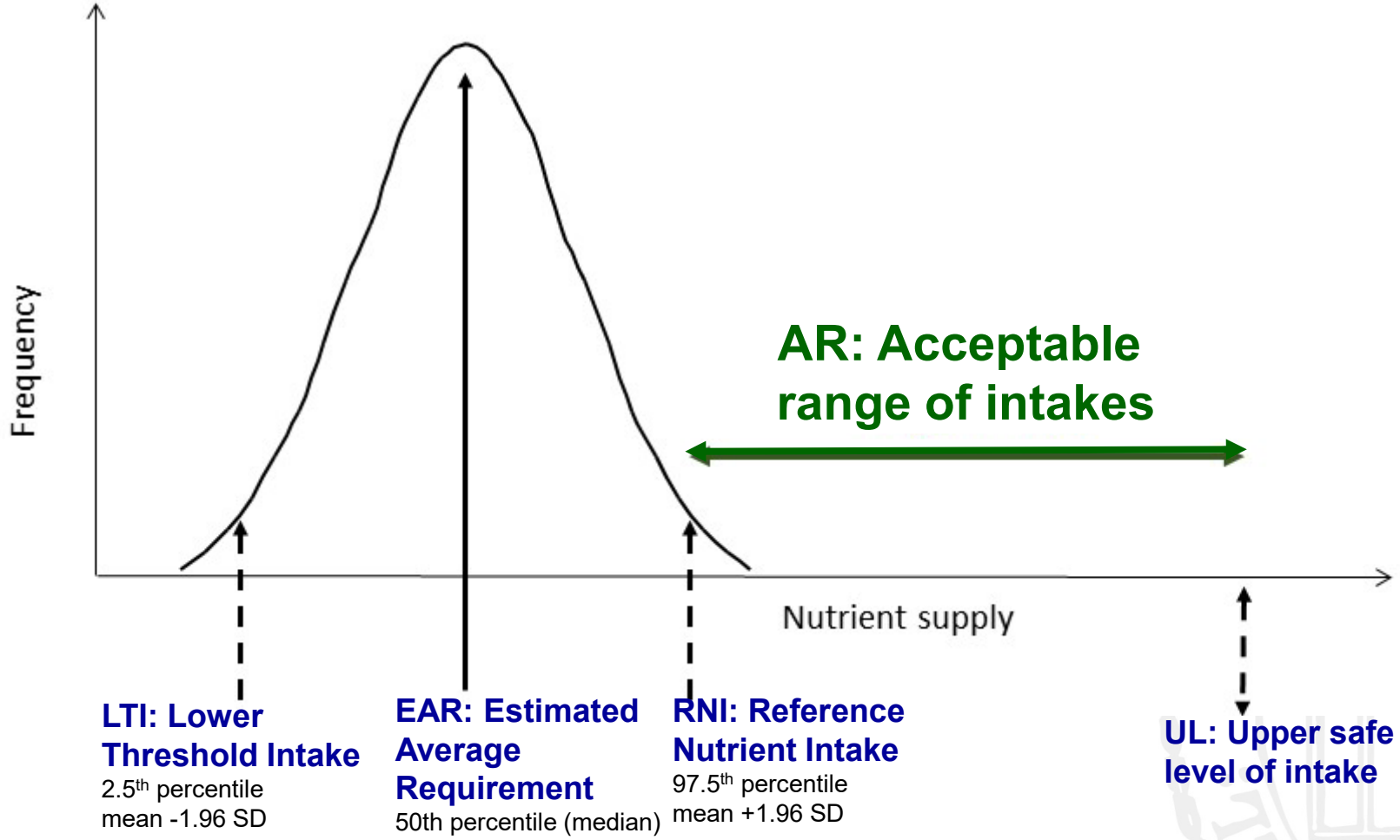
Level of consensus	Support (% votes)
Strong consensus	>95 %
Consensus	>75-95 %
Majority support	>50-75 %
No consensus	<50 %

Old and New RNIs for Preterms

Nutrient	Current recommendation per kg/day	Current recommendation per 100 kcal	Previous edition 2014, per kg/day	Previous edition 2014, per 100 kcal
Fluids, mL [A]	135–200	-	135–200	-
Energy, kcal [A]	110–130	-	110–130 (*85–95 i.v.)	-
Protein, g [B]	3.5–4.5	3.2–4.1	3.5–4.5	3.2–4.1
Lipids, g [B]	**4.55–8.1**	**4.1–4.7**	4.8–6.6	4.4–6
Carbohydrate, g	11.6–13.2	10.5–12	11.6–13.2	10.5–12
Phosphorous, mg [A]	**70–120**	**64–190**	60–140	55–127

Superscript letters indicate the level of support by the group of authors of this book: A, strong consensus (supported by >95%); B, consensus (>75–95%).
*Parenteral multivitamin preparations may only provide 160 IU vitamin D/kg until the infant reaches 2.5 kg.

Reference Nutrient Intake Values for populations of preterm infants



Koletzko B et al, Defining nutritional needs of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

The needs of individual preterm infants may differ

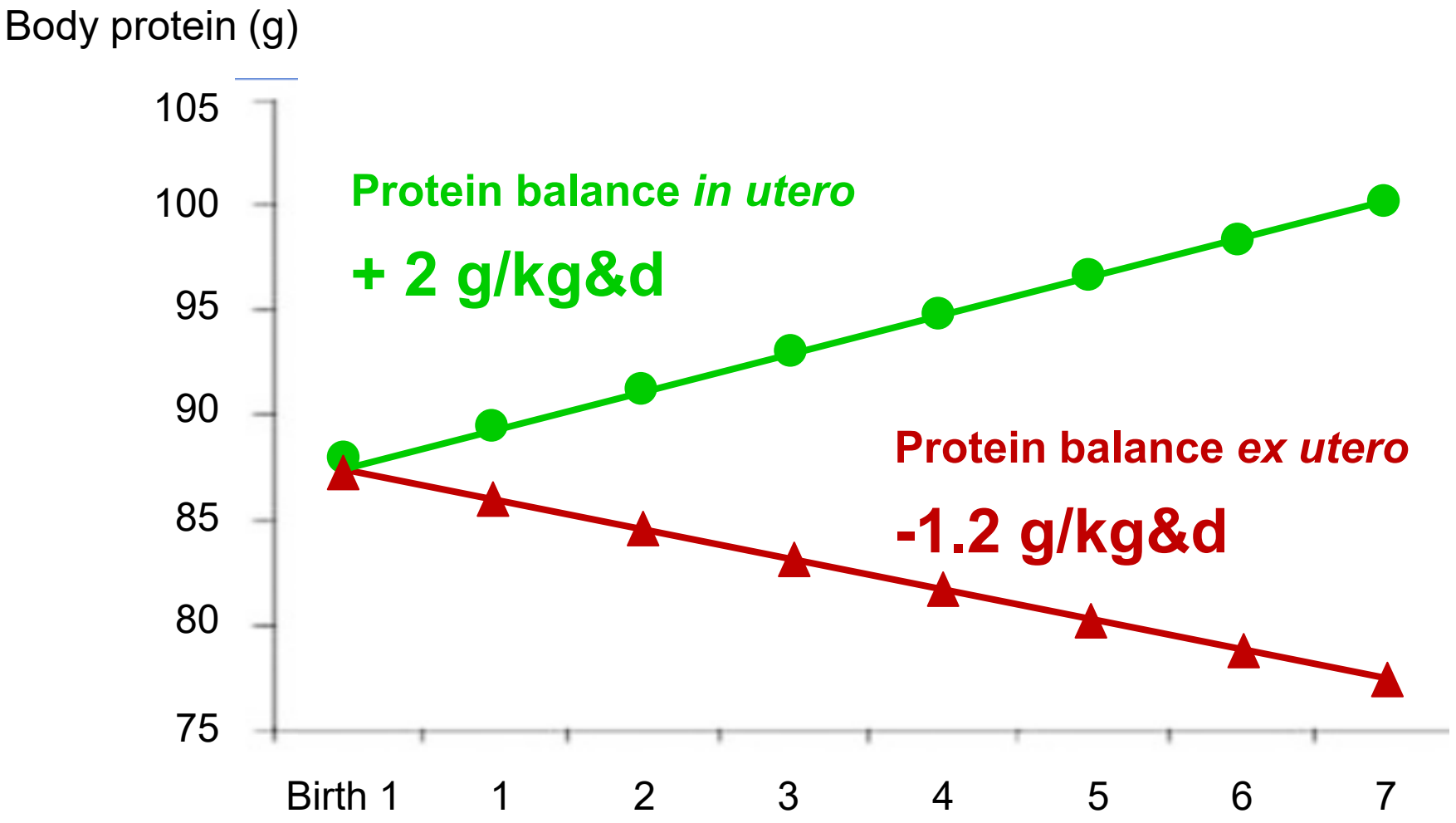
Individual needs may differ with

- Gestational age
- Postconceptional age
- Birth weight / body stores at birth
- Rates of weight gain / current weight
- Disease conditions
- Other factors

Koletzko B et al, Defining nutritional needs of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Importance of early supply

Fetal amino acid supply via the placenta ≈3.5-4.0 g/kg&d



Fetal accretion, wk 26

Preterm, glucose i.v. :

≈22% body protein lost in 1 week

Denne SC & Poindexter BB, Sem Perinat 2007; Embleton ND & v d Akker CHP, Sem Perinat 2019.

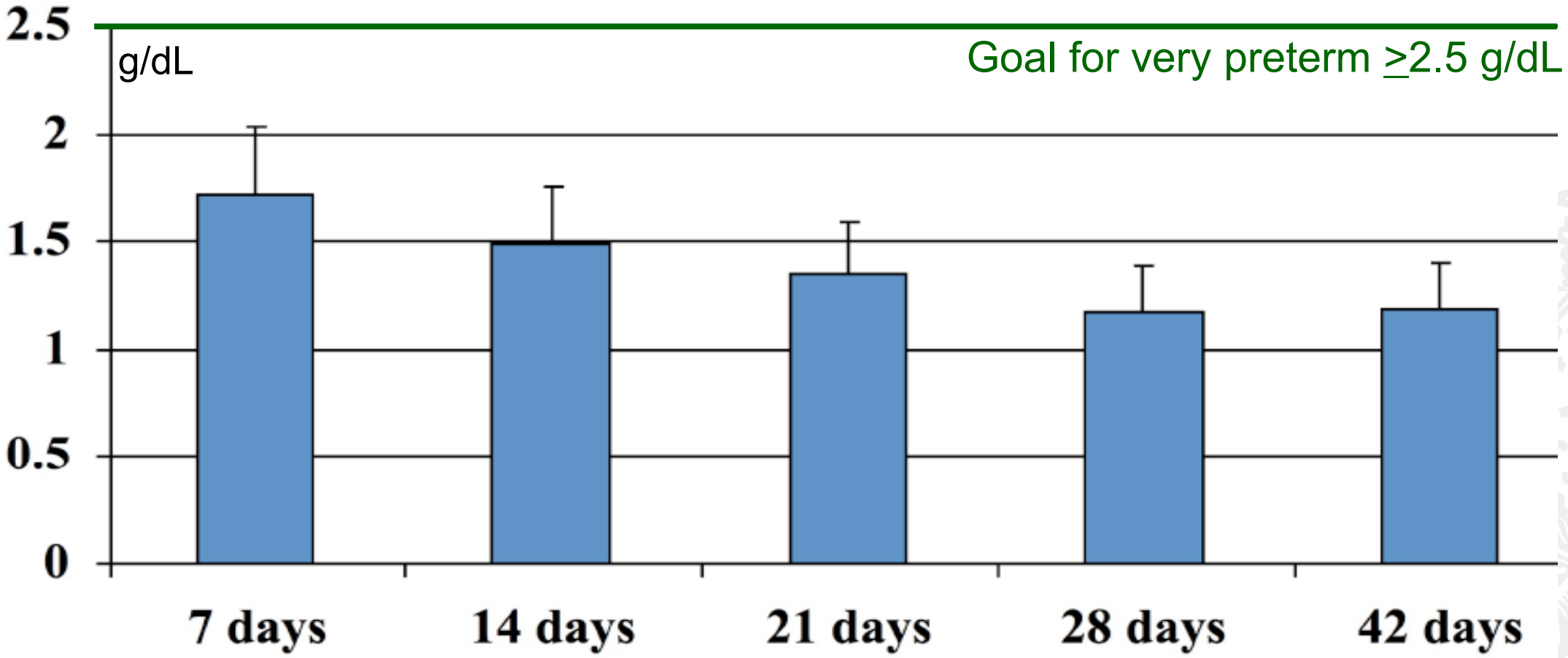
Protein Requirements of Preterm Infants

Current body weight	g/kg&d
500–1500 g	3.5–4.5 (max. 3.5 i.v.)
1500–2000 g	3.0–4.0 (max. 3.0 i.v.)
2000–2500 g	2.5–3.5 (max. 2.5 i.v.)

v d Akker, CHP, et al. Proteins and Amino Acids. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger. 2021. Table modified from appendix.

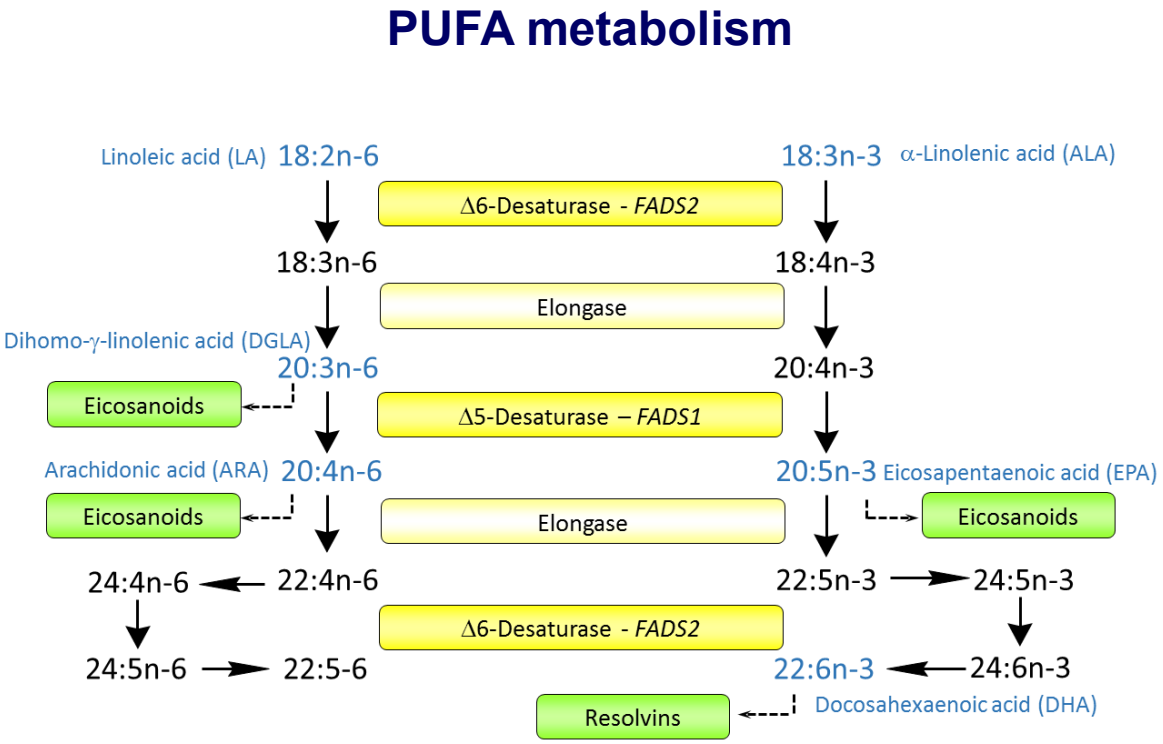
Protein in preterm own mothers' milk too low and falls over time ➔ add protein fortifier

@reaching 50-100 ml/kg&d



from Ziegler E, based on data by Lemons et al 1982
in Koletzko B et al (eds.): Nutritional Care of the Premature Infant, 1st. ed. 2014

PUFA and LC-PUFA (DHA & ARA)



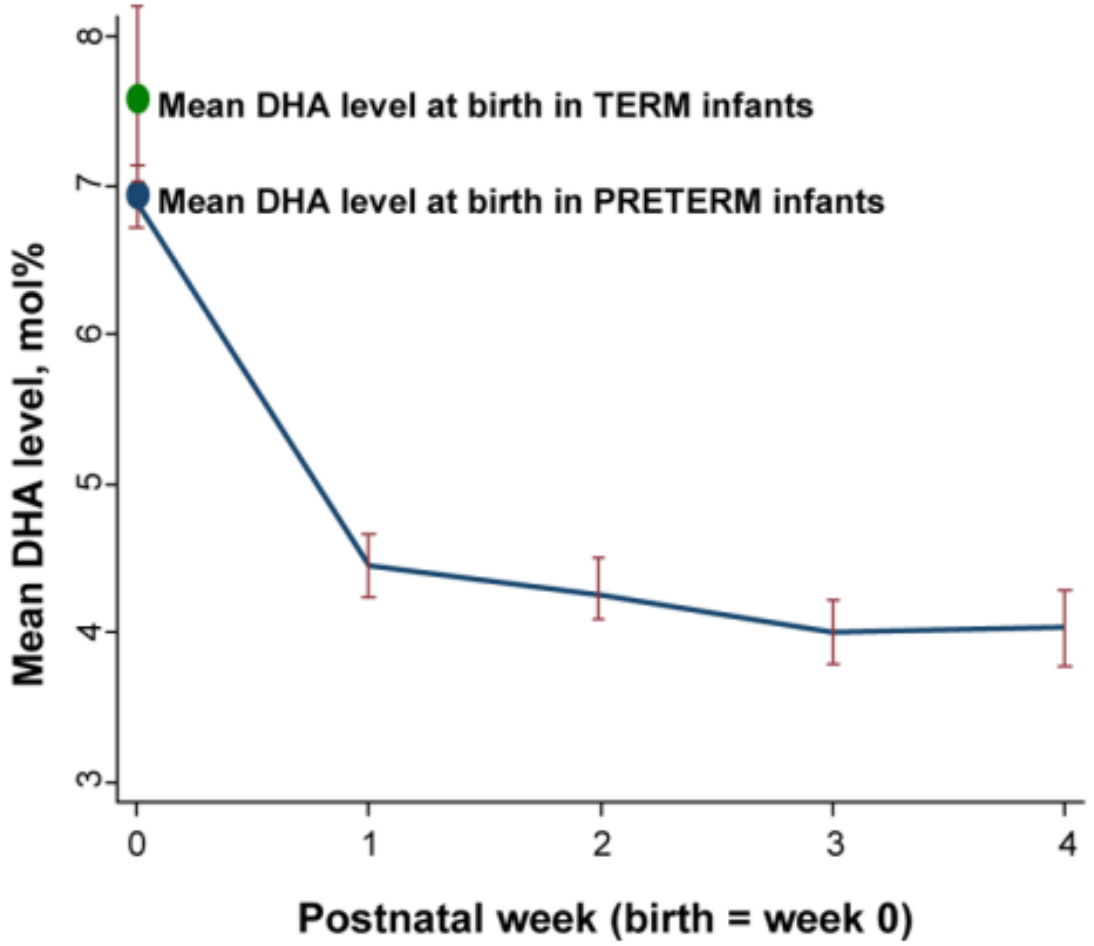
- ω-6 linoleic acid and ω-3 α-linolenic acids = essential nutrients
- Very preterms synthesize less ω-6 and ω-3 LC-PUFA (ARA, DHA) than needed for growth
- DHA intakes ≈1% of fatty acids along with ARA to match fetal accretion
- RCTs: some report benefits for visual & mental development, and ↓ ROP

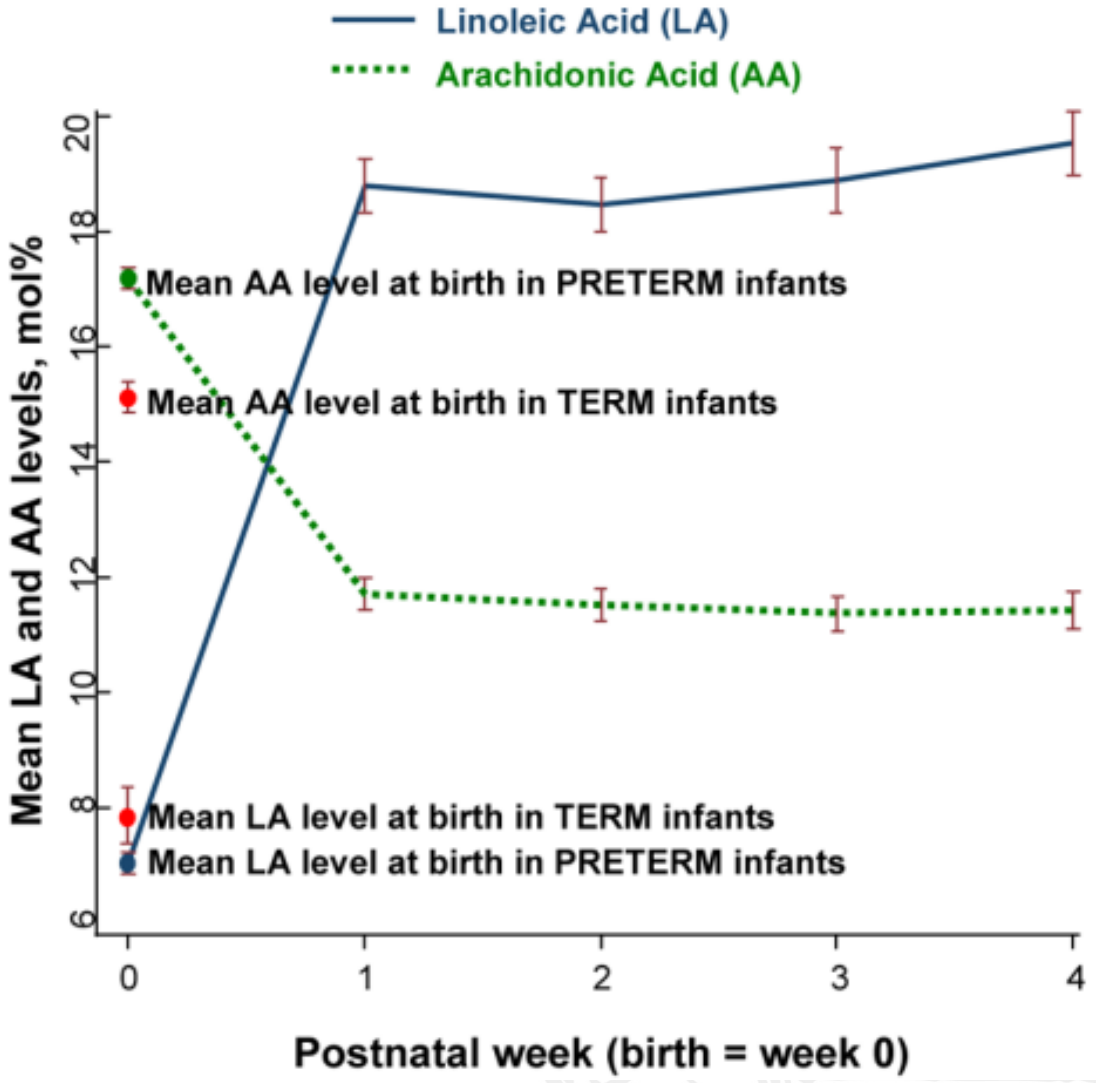
Koletzko B, Lapillonne A. Lipid requirements of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dr. von Hauner Children's Hospital Univ. Munich

Rapid postnatal fall of plasma DHA & ARA in preterms





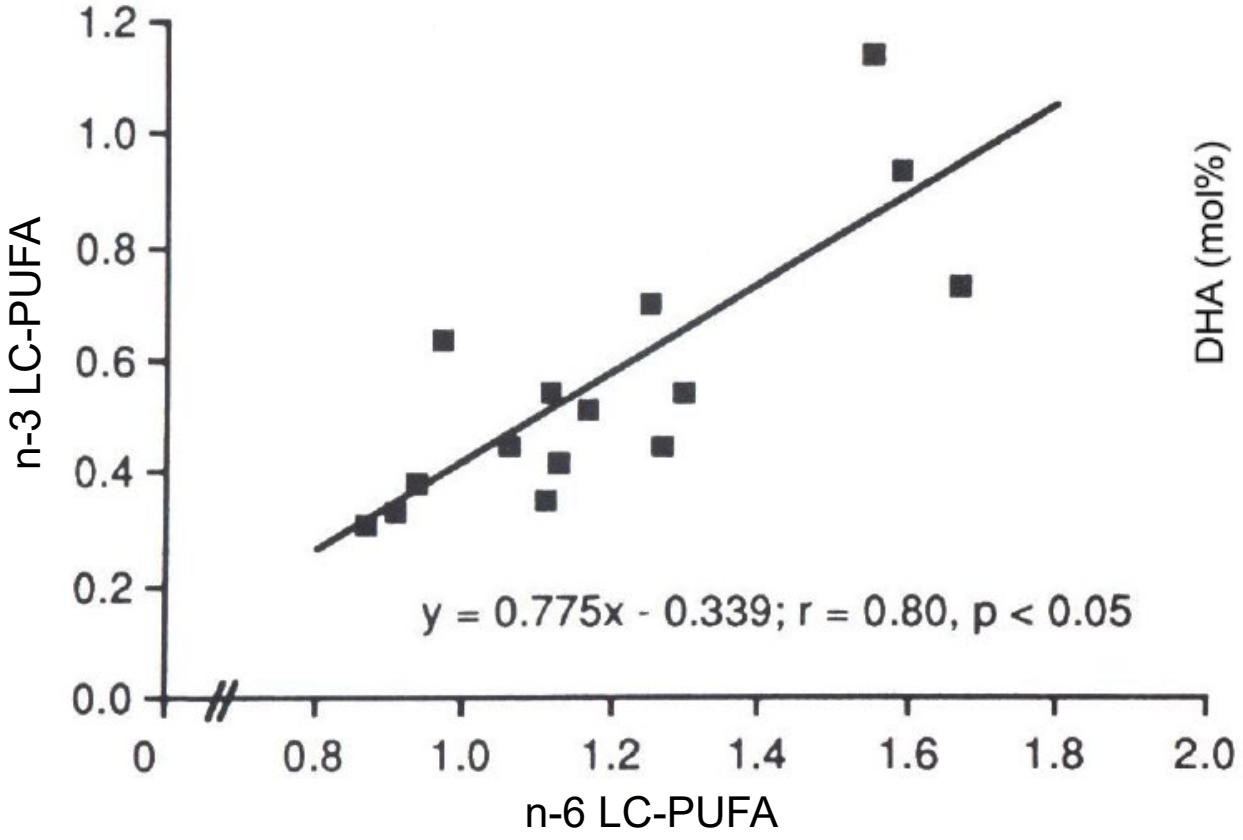
Martin CR et al. J Pediatr. 2011 Nov;159(5):743-749.e1-2. doi: 10.1016/j.jpeds.2011.04.039.

Human milk provides ARA & DHA which are correlated

Milk for term infants

Germany

Mean ARA:DHA ratio 1.8

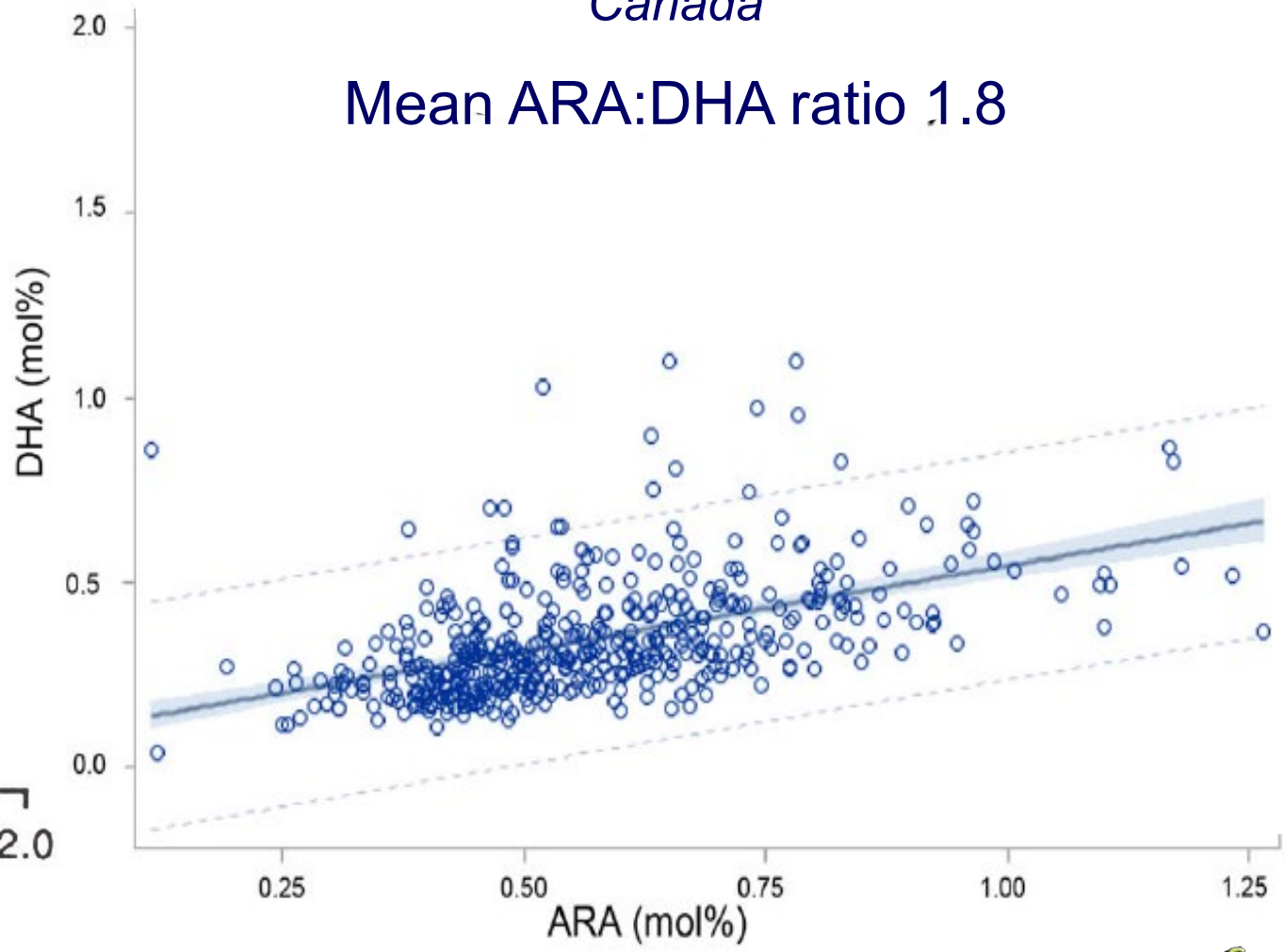


Koletzko B et al, Am J Clin Nutr 1988;47:954-9.

Milk for preterm infants

Canada

Mean ARA:DHA ratio 1.8



Hopperton KE et al, Lipids. 2022. doi: 10.1002/lipd.12338.

Human milk provides LC-PUFA (DHA & ARA)

- Preterm infants deposit much DHA & ARA in brain and other tissues, with functional importance. Fetal accretion >> term infants
  ⇨ preterms need ≈30-65 mg DHA/kg & 50-130 mg ARA/kg/day
- Mothers providing breast milk: to enhance milk DHA **eat oily fish**, take **DHA supplements** *(e.g. ≈1 g/d)*
- Preterm formula should provide 0.5-1 % of fat as **DHA**, with **ARA ≥ DHA** (ARA:DHA ratio = 1-2)

Koletzko B, Lapillonne A. Lipid requirements of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Lipid supply to preterm infants

Substrate	Advisable supply
Total fat	4.1-7.4 g/100 kcal *(≈37-67 E%)*
Medium chain triglyc. *(MCT)*	≤40 % of fat
ω-6 Linoleic acid	350-1400 mg/100 kcal
ω-3 α-linolenic acid	>50 mg/100 kcal
ω-3 DHA	0.5-1 % of fatty acids
ω-3 DHA:ω-6 ARA-ratio	0.5 to 1
Total choline *(free & bound)*	≥30 mg/100 kcal
L-carnitine	≥1.5 mg/100 kcal

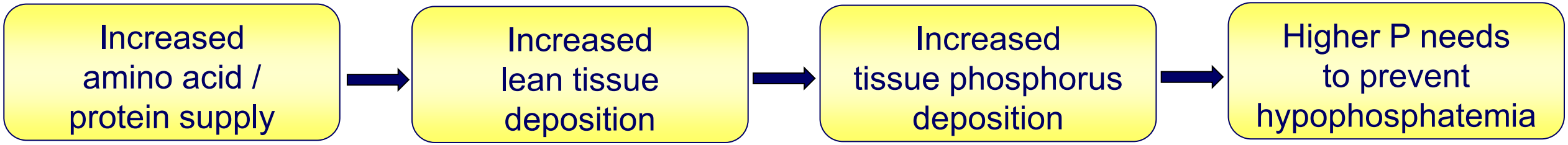
Koletzko B, Lapillonne A. Lipid requirements of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Phosphorus

More than bone health	• Essential for cellular energy metabolism, along with Ca & Mg • Important for cardiac, respiratory, and neurological function
Physiology	• Skeleton (85–88%), cell membranes, nucleic acids, glucose metabolism, energy (adenosine triphosphate), oxygen-hemoglobin dissociation curve (2,3-diphosphoglycerate)
Clinical Monitoring	• **Normal range:** 5.6–6.1 mg/dL (1.8–2.6 mmol/L) • **Deficiency:** <4 mg/dL (<1.3 mmol/L) • **Severe deficiency** <2.5 mg/dL (<0.8 mmol/L)

Taylor SN. Calcium, Magnesium, Phosphorus, and Vitamin D. In: Koletzko B, Cheah F-C, Domellöf M, Poindexter BB, Vain N, van Goudoever JB (eds): Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines. World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

Phosphorus needs depend on growth & protein supply



Recommended P supply

	mmol/kg&d	mg/kg&d
First postnatal days i.v.	1-2	31-62
After first days i.v.	1.25-3 *	31-93
Enteral	2.3-3.9	70-120

**Max. often limited to 1.5- 2) due to solubility and molar ratio with Ca*

Taylor SN. Calcium, Magnesium, Phosphorus, and Vitamin D. In: Koletzko B, Cheah F-C, Domellöf M, Poindexter BB, Vain N, van Goudoever JB (eds): Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines. World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

Advisable daily enteral nutrient intakes per kg body weight for preterm infants by body weight categories

	Current body weight category			
	500 – ≤1000g	1000 – ≤1500g	1500 – ≤2000g	2000 – ≤2500g
Enteral fluid intake, mL/kg				
First day of life[B]	10–30	20–40		
Daily increment	10–30[B]	20–40[A]		
Energy, kcal/kg[A]	110–130		105–125	
Protein, g/kg[B]	3.5–4.5	3.5–4.5	3.0–4.0	2.5–3.5
Carbohydrates, g/kg[B]	11–13			
Iron, mg/kg[B]		2–3 from 2 weeks	2 from 2-4 weeks	1–2 from 4-6 wks

Superscript letters indicate level of support by the writing group: A=strong consensus (supported by ≥95%); B=consensus (≥75–95%); C=majority support (≥50–75%); D=no consensus (<50%).

Koletzko B, Wieczorek S, Cheah FC, et al. Recommended Nutrient Intake Levels for Preterm Infants. In: Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines. Koletzko B, et al. (eds): World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

How to approach meeting RNI in very preterm infants?

- Supplemental parenteral nutrition from day 1
- Start with 1.5–2.5 g amino acids/kg&d, increase to 3.5 g/kg&day in the next few days (with sufficient other macro- and micronutrients)
- Enteral feeding preferably with own mother's milk plus fortifier, goal to reach at least 3.5-4.0 g protein/kg&day (with sufficient other macro- and micro-nutrients); increase up to 4.5 g/kg&d with growth faltering
- Parenteral amino acid intake should not be tapered before an enteral intake of at least 75 mL/kg/day has been reached

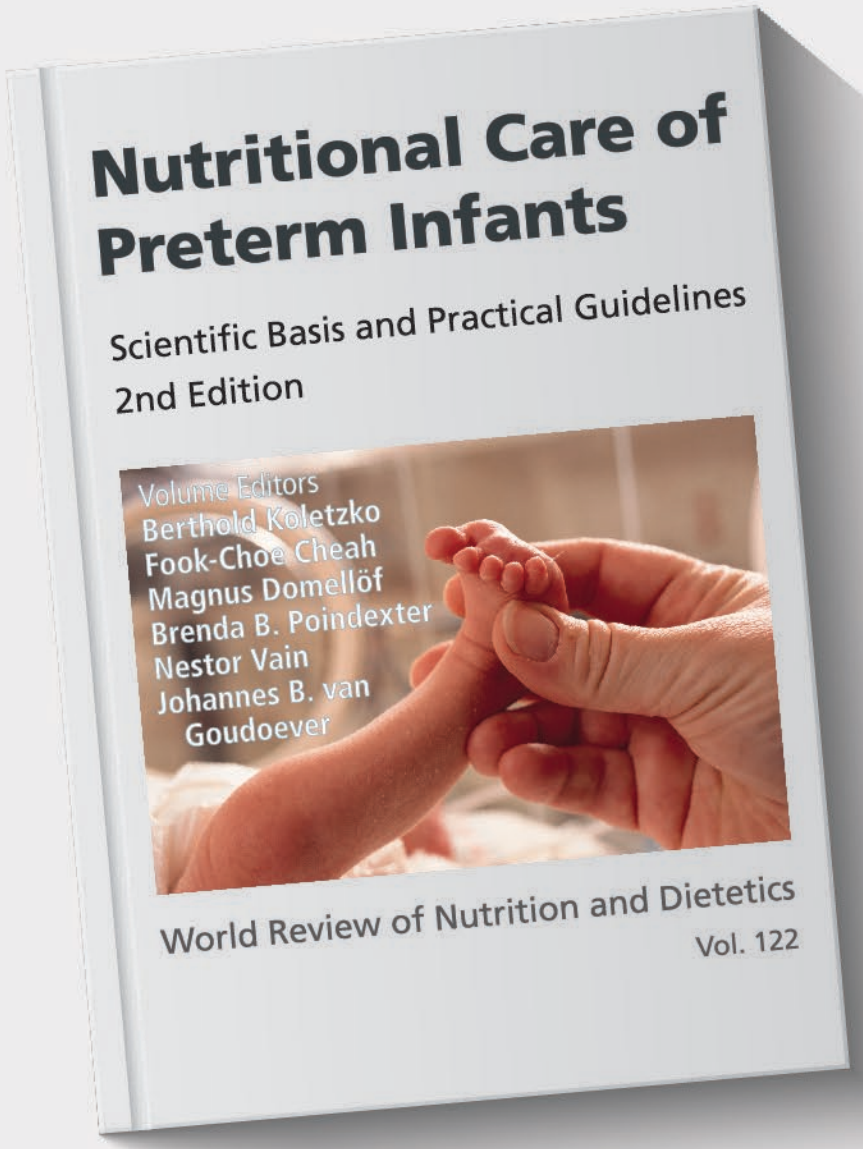
Take-home messages: RNI

- Reference nutrient intakes (RNI) refer to stable growing preterm infant populations according to current body weight categories
- For most nutrients, needs are proportional to growth rate
  (few exceptions e.g. water, fat)
- Nutrient intakes below RNI may be appropriate during the early postnatal phase prior to full feeding, and during critical illness
- Needs of an individual preterm infant may markedly deviate from population reference intakes

Koletzko B et al, Defining nutritional needs of preterm infants. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.

Research opportunities: RNI

- Great opportunities to reduce the knowledge gap on nutrient needs in different subgroups of preterm infants
- Application of current methods and technologies can limit the burden on preterm infants participating in such studies
- Neonatologists, researchers and funding agencies should invest in studies to advance solid knowledge on optimal nutrition of preterms, to support their optimal health and development



Human Milk Fortification for Preterm Infants: A Review

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Berthold Koletzko, MD, PhD

Berthold Koletzko tends to be biased towards breastfeeding as member of the German National Breastfeeding Committee, Chair Nutrition Committee, German Paediatric Society, and Past-President, Int Soc Research on Human Milk & Lactation. LMU - Ludwig Maximilians Universität Munich and its employee BK received support for scientific and educational activities from the European Union (EU) Programmes DYNAHEALTH-633595, Lifecycle-733206 and CoreMD 965246, EU Research Council Advanced Grant META-GROWTH ERC-2012-AdG–no.322605, EU Erasmus+ Early Nutrition eAcademy Southeast Asia-573651-EPP-1-2016-1-DE-EPPKA2-CBHE-JP and Capacity Building to Improve Early Nutrition and Health in South Africa-598488-EPP-1-2018-1-DE-EPPKA2-CBHE-JP, EU Interreg Focus in CD-CE111, EU Danube CD-Skills DTP3-572-1.2, EU Joint Programming Initiative HDL projects NutriPROGRAM, EndObesity and BiomarKids, German Ministry of Education and Research 01EA1904 and 01 EA 2101, German Ministry of Health 1503-68403-2021, German Research Council Ko912/12-1 and INST 409/224-1 FUGG, Alexander von Humboldt Foundation 3.3 - 1218469 - POL - HFST-E, US National Institutes of Health 1R03HD087606-01A1, Else Kröner Fresenius Foundation, Family Larsson Rosenquist Foundation, and healthcare and nutrition companies i.e. Bayer, Barilla, Danone, DGC, DSM, Hipp, Nestlé and Reckitt. BK is the Else Kröner Seniorprofessor of Paediatrics at LMU University of Munich, financially supported by Else Kröner-Fresenius-Foundation, LMU Medical Faculty and LMU University Hospitals.

The grantor, Mead Johnson Nutrition, had no involvement in selecting faculty, editorial decisions, content or writing of this educational material.

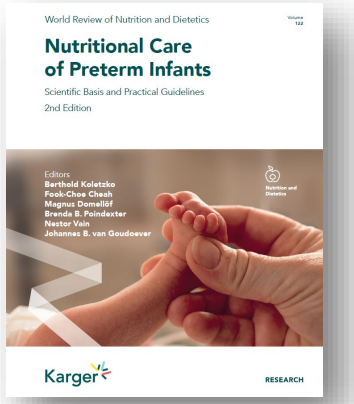
Fortified mother's own milk = preferred choice f. preterms

- Associated with faster establishment of full enteral feeding, infection protection, parental bonding, better cognitive outcomes, etc.
- Strong evidence: risk reduction for NEC (necrotizing enterocolitis)
- Next best choice: donor human milk from a milk bank with established safety standards—but not the same benefit as MOM

Koletzko B, Cheah F-C, Domellöf M, Poindexter BB, Vain N, van Goudoever JB (eds): Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines. World Rev Nutr Diet. Basel, Karger, 2021, vol 122, pp 212–224 (DOI: 10.1159/000514733)

Mother's Own Milk and Donor Milk

Regina Valverde[a] Nestor Alejandro Dinerstein[b] Nestor Vain[c]



American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Promoting Human Milk and Breastfeeding for the Very Low Birth Weight Infant

Margaret G. Parker, MD, MPH,[a] Lisa M. Stellwagen, MD,[b,c] Lawrence Noble, MD,[d,e] Jae H. Kim, MD, PhD,[f] Brenda B. Poindexter, MD,[g] Karen M. Puopolo, MD, PhD,[h] SECTION ON BREASTFEEDING, COMMITTEE ON NUTRITION, COMMITTEE ON FETUS AND NEWBORN

Valverde R et al, In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger, Basel, 2nd. ed. 2021, World Rev Nutr Diet 122.
American Academy of Pediatrics. Peds. 2021148:e2021054272.

Feeding human milk reduces NEC risk

- 12 RCTs or quasi-RCTs comparing feeding with formula versus donor breast milk in 1879 preterm or LBW infants
- Formula feeding (vs. human milk):

RR NEC: 1.87 *(95% CI 1.23 to 2.85)*

NNT for 1 NEC case: 33 *(95% CI 20 to 100)*

THE COCHRANE COLLABORATION

Quigley M et al, Cochrane Database of Systematic Reviews 2019.

Donor milk ≠ mother's own milk

Preterms 22–36 wks PCA before (n=139) vs. after (183) donor human milk bank

	No donor milk	Donor milk	P
Feed advance, ml/kg&d	7.4±3.5	9.9±4.5	<0.001
Time to full enteral feeds, d	21.0 (14.5–31.0)	20.0 (14.0–28.0)	n.s.
Time to regain bw, d	11.0 (8.0–14.0)	8.0 (3.0–11.0)	<0.001
SDS weight, 37 wks/discharge	−1.5 ± 0.8	−1.9 ± 0.7	<0.001

Donor milk ⇨ **lower weight gain**

Wu T et al, Mat Child Nutr. 2002, 18 Jan. DOI: 10.1111/mcn.13319.

Own mother's vs. donor milk: growth differs

- Single-center retrospective study, 314 infants ≤32 wks GA or ≤1800 g with NICU stay ≥7 days fed fortified human milk

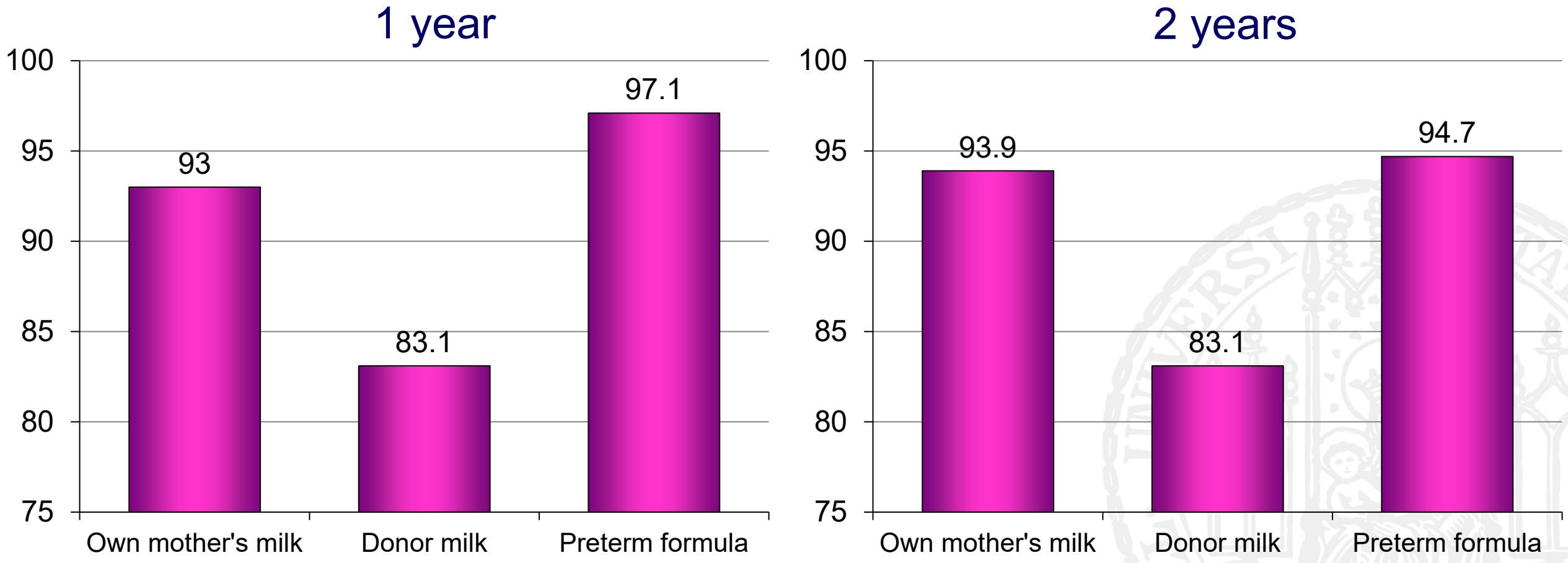
- Per **+10% more donor human milk** vs. own mothers' milk **-0.17 g/kg&d weight gain** to 36 weeks GA or NICU discharge

- Per **+10% more donor human milk** vs. own mothers' milk **-0.01 cm/wk** adjusted **head circumference**

Brownell et al, JPGN 2018;67:90-6. doi: 10.1097/MPG.0000000000001959.

Cognition: donor vs. own mother's milk differ

Bayley III cognition scores at corr. age



81 preterms, GA 27,1 wks, Tufts Med Center Boston. Donor milk from Mother's Milk Bank of New England

Madore et al, Clin Ther 2017.

Mother's own milk = preferred choice

- **Initiate** milk expression **soon after birth**
  RCT, 180 mothers: no diff. with first expression at 1, 1–6 or 3–6 h after birth

- **Frequent milk expression** *≥4–7 times/day*
  ⇨ longer duration of milk production, greater milk volumes

- **Discourage informal milk sharing**
  Risk of contamination with infectious agents, drugs; suboptimal handling/storage

- **Establish NICU protocols** and **parent education** on milk pump handling/cleaning, milk storage, handling & transport

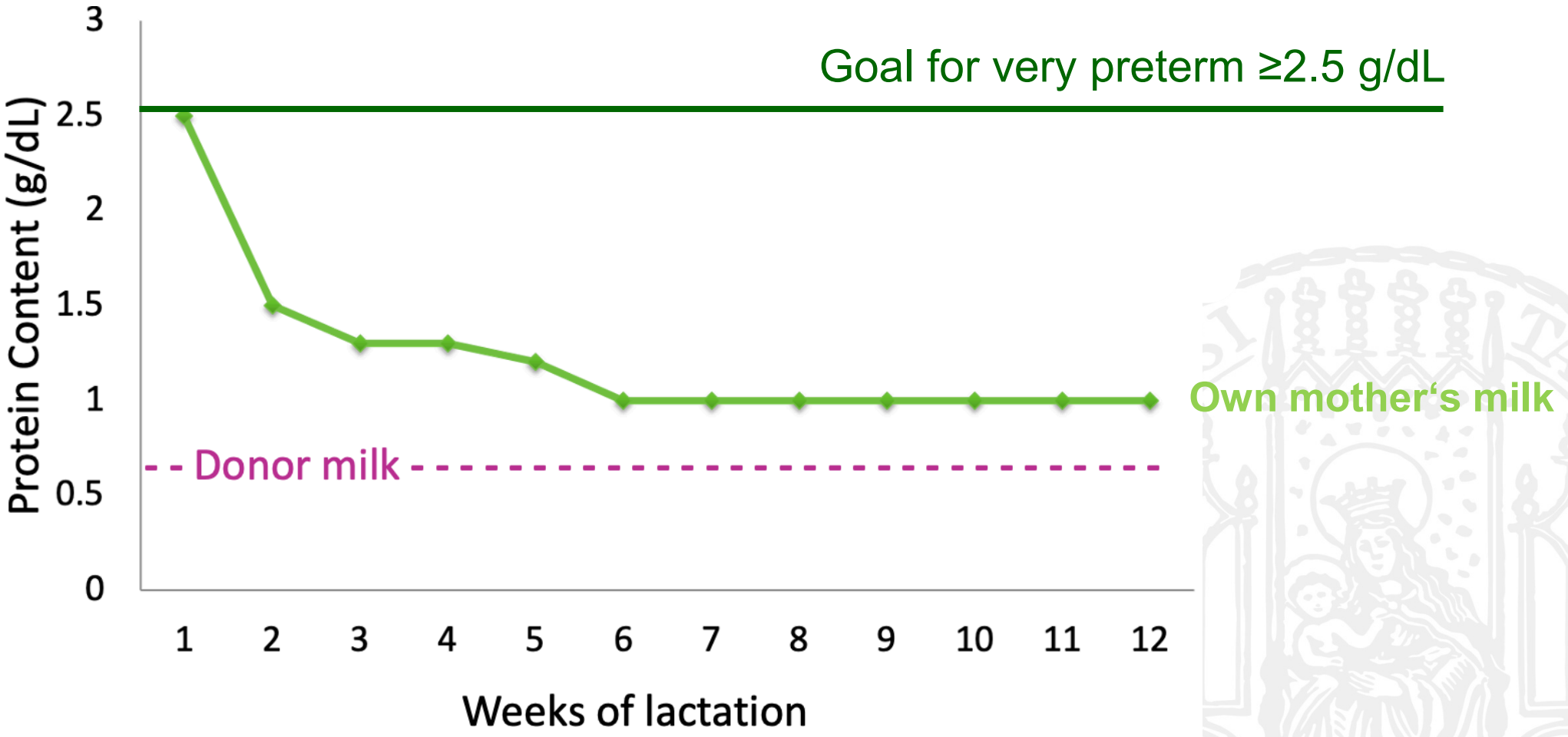
Am Acad Pediatrics. Peds. 2021;148:e2021054272.

Human milk fortification is required to meet the high protein requirements of preterm infants

Current body weight	g/kg&d
500–1500 g	**3.5–4.5** (max. 3.5 i.v.)
1500–2000 g	**3.0–4.0** (max. 3.0 i.v.)
2000–2500 g	**2.5–3.5** (max. 2.5 i.v.)

v d Akker, CHP, et al. Proteins and Amino Acids. In: Koletzko B et al (eds). Nutritional Care of Preterm Infants. Karger. 2021. Table modified from appendix.

Protein in preterm own mothers' milk is too low, falls over time, and is highly variable



Poindexter B, PAS 2021

Protein fortification of human milk improves growth in preterm infants

Protein fortification of human milk (6 RCTs, 204 preterms)

- Improved gain of **weight** (Δ 3.82 g/kg/day, 95% CI 2.94–4.7), **length** (Δ 0.12 cm/wk, 95% CI 0.07–0.17), and **head circumference** (Δ 0.06 cm/wk, 95% CI 0.01–0.12)
- NEC risk unchanged (RR 1.11, CI 0.07–17.12)

THE COCHRANE COLLABORATION

Amissae EA et al, Cochrane Database Syst Rev 2018.

Why fortify, for whom?

Why fortify [1]

- Avoid postnatal growth faltering
- Avoid deficits in minerals and micronutrients
- Support linear growth & bone mineralization
- Further neurocognitive development

For whom

- Very preterm infants (<32 weeks)
- Preterm infants <1,800 g
- Preterm infants requiring fluid restriction

Targeted outcomes

- Meet nutrient needs
- Growth rates approaching fetal growth
- Reduced growth faltering and associated adverse effects

Special challenges to be avoided

- Low weight gain ⇨ higher risk of later metabolic disorders and NCDs [2,3]
- Low head growth ⇨ motor / cognitive delay [4,5]
- Postnatal growth faltering [6,7]

SD, standard deviation

1. Arslanoglu S, et al. Front Pediatr. 2019;7:76; 2. Embleton ND, et al. Arch Dis Child. 2016;101:1026–31; 3. Barker DJ, et al. N Engl J Med. 2005;353: 1802–9; 4. Cooke RW, et al. Arch Dis Child. 2003;88:482–7; 5. Raghuram K, et al. Pediatrics. 2017;140:e20170216; 6. Fenton TR, et al. BMC Pediatr. 2013;13:59; 7. Rochow N, et al. Pediatr Res. 2016;79:870–9.

Available products to fortify or supplement human milk

Multicomponent fortifiers	Bovine milk derived multicomponent fortifiers
	Human milk derived multicomponent fortifiers
Single-nutrient supplements	Protein
	Fat
	• Medium-chain triglyceride emulsions
	• Long-chain fatty acid emulsions
	• HM-derived cream
	Carbohydrates
	• Glucose polymers and maltodextrins
Formulas for preterm infants	Preterm formula
	Postdischarge formula

Adapted from Table 2, Picaud JC, Vicent M, Buffin R. Human Milk Forticificaiton for Preterm Infants: A Review. In: In: Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines. Koletzko B, et al. (eds): World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

Types of Fortifiers

Powder fortifiers	Add 0.8–1.6 g protein/100 mL HM
Liquid fortifiers (based on bovine milk protein)	Add 1.0–1.8 g protein/100 mL HM
Hydrolyzed-protein fortifier	Possible benefits under discussion
HMF with carbohydrates and/or fats	Increase energy content to 67–80 kcal/100 mL

Picaud JC, Vicent M, Buffin R. Human Milk Forticificaiton for Preterm Infants: A Review. In: In: Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines. Koletzko B, et al. (eds): World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

When and How to Start Human Milk Fortification?

When to start?	• No consensus about best time to start fortification—add full-strength at 50–100 ml/kg&d enteral feed
Why wait?	• Don’t wait, no benefit from delayed start but risk of slower growth
Full strength?	• No demonstrated advantage of starting at less than full-strength fortification
Safe?	• Safe when introduced early with enteral feeds, not associated with feeding intolerance

Picaud JC, Vicent M, Buffin R. Human Milk Forticificaiton for Preterm Infants: A Review. In: In: Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines. Koletzko B, et al. (eds): World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

Benefits of Starting Early [1–3]

Study results with standardized fortification

- Starting early with HMF improved postnatal growth
- Fortification considered “early” when started at 20–60 mL/kg&d enteral feeds
- Starting before 60 mL/kg/day enteral feeding volume may benefit infants of 500–1,250 g birth weight, improving body weight and head circumference gain [1]
- No increase in complications, such as feeding intolerance or NEC
- Cochrane meta-analysis on fortification at 20 or 40 mL/kg/day vs. 100 mL/kg&d enteral feeds: insufficient evidence to support or refute early HM fortification [3]

NEC, necrotizing enterocolitis.

1. Godden B, et al. *J Paediatr Child Health.* 2019;55:867–72.
2. Huston RK, et al. *J Neonatal Perinatal Med.* 2020;13:215–21.
3. Thanigainathan S, et al. *Cochrane Database Syst Rev.* 2020; 7:CD013392.

No evidence for benefit of human milk-based over cows' milk-based fortifiers

- **No benefit** demonstrated for human milk- vs. bovine milk-derived fortifier in human milk-fed preterm infants
- Low-certainty evidence from 1 study in human milk-fed preterm infants suggests no **change in risk of NEC, mortality, feeding intolerance, infection, or growth** with that human milk- vs. bovine milk-derived fortifiers

Premkumar MH et al, Cochrane Database of Systematic Reviews 2019.

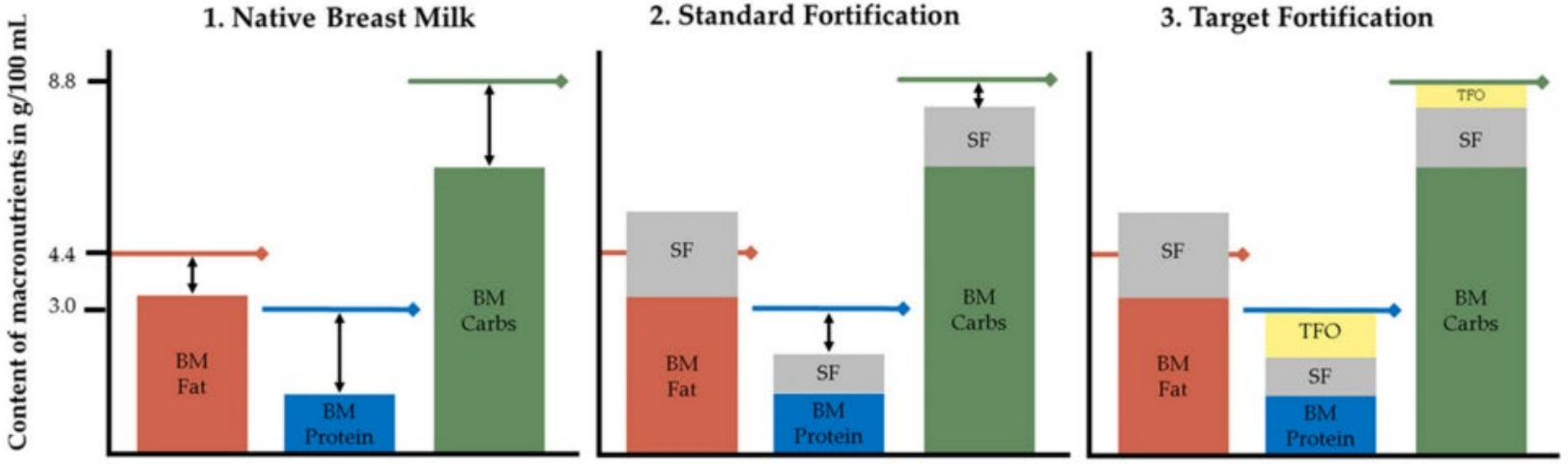
Which Fortification Strategy?

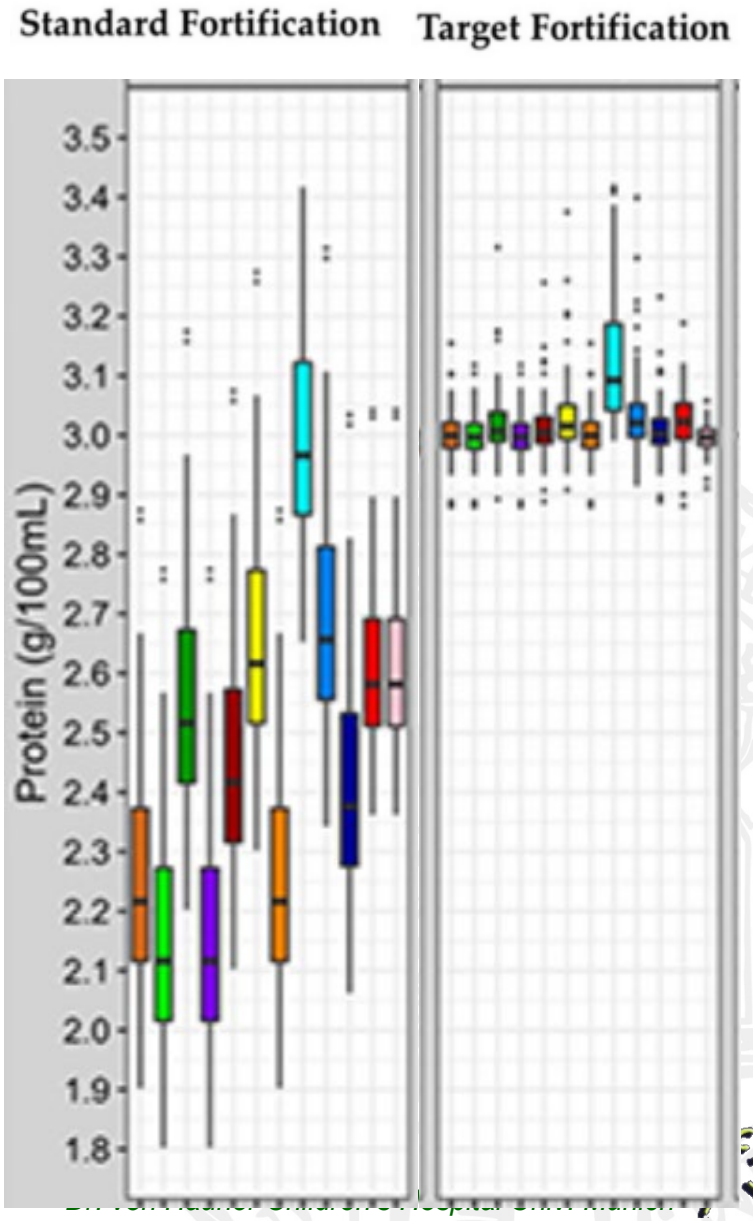
Standardized	• Improves postnatal growth, bone mineralization; but does not achieve adequate postnatal growth in all very preterm infants
Adjusted Fortification	• Fortifier dose/protein intake adjusted based on weight gain and/or blood urea nitrogen • Studies report higher weight and head circumference gains compared to standardized fortification group [1,2]
Targeted	• Adjust dose to measured composition of HM [3–5] • Safe, apparent benefit over standardized fortification [6,7]

- Adjustable and targeted fortifications promote postnatal growth in very preterm infants compared to standardized fortification. Long-term effects still need to be evaluated.

1. Arslanoglu S, et al. J Perinatol. 2006;26:614–21; 2. Alan S, et al. Early Hum Dev. 2013;89: 1017–23; 3. Buffin R, et al. J Perinatol. 2017;37:552–7; 4. Fusch G, et al. Clin Perinatol. 2017;44:209–67; 5. de Halleux V, et al. Arch Pediatr. 2007;14 Suppl 1:S5–10; 6. Rochow N, et al. Clin Nutr. 2020;S0261–5614:30202–8; 7. AAP. Breast feeding. In: Kleinman RE, Greer FR, eds, Pediatric nutrition. 7th ed. Elk Grove Village: American Academy of Pediatrics; 2014:41–60.

Targeted fortification based on HM analysis improves intake





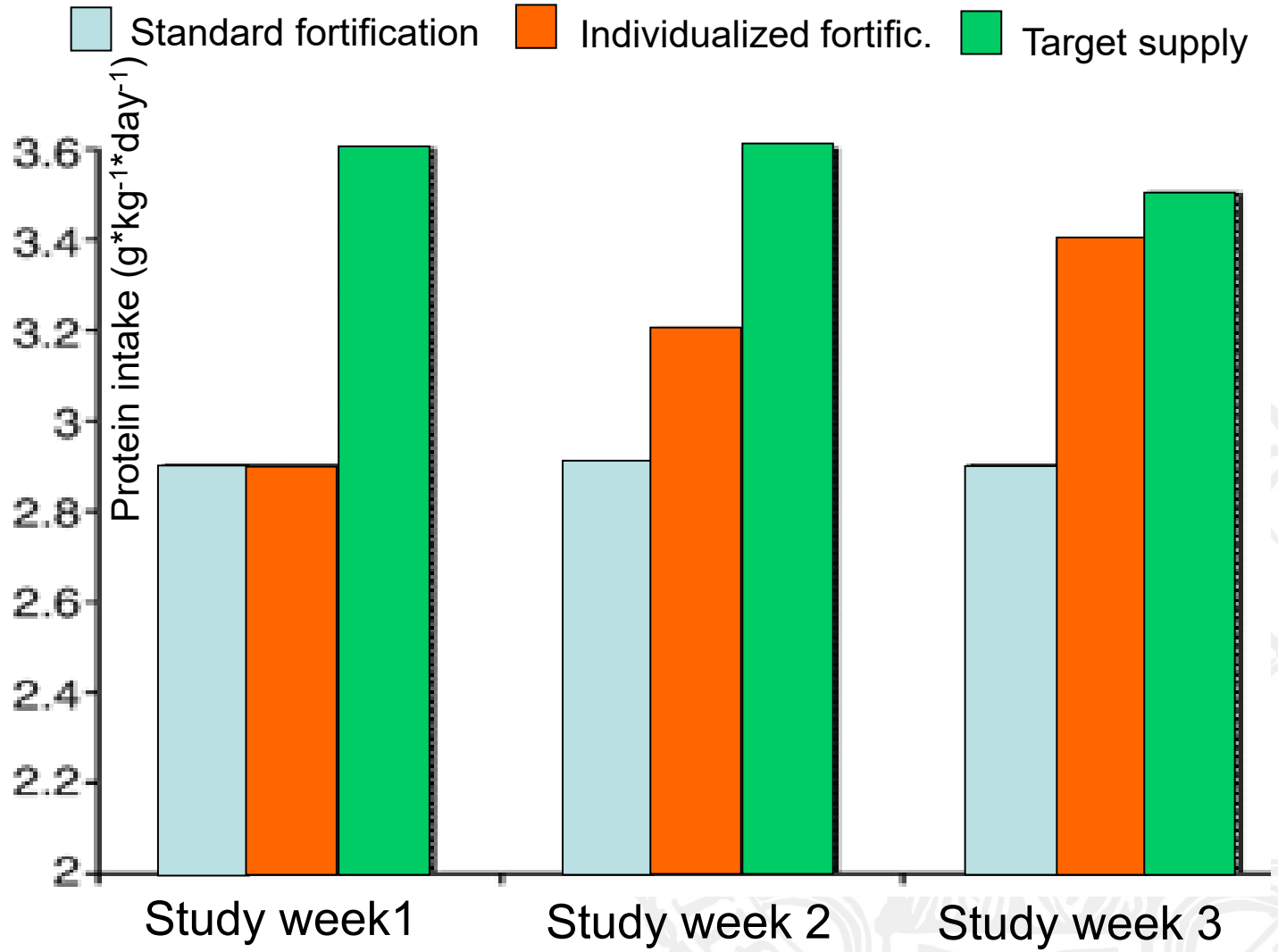
Fusch S et al, Front Nutr.. 2021 Sep 21;8:652641. doi: 10.3389/fnut.2021.652641.

Adjusted fortification based on BUN enhances supply

Start standard fortification, 2x/wk blood urea nitrogen (BUN)

BUN mg/dL	BUN mmol/L	Adjustment
9-14	3.2-5	None
<9	<3.2	+1 Level
>14	>5	-1 Level

Fortification	g HMF/100 ml
3	6.25 + 0.8 prot
2	6.25 + 0.4 prot
1	6.25
0	5
-1	3.75
-2	2.5



Arslanoglu et al, J Perinatol 2006.

Dr. von Hauner Children's Hospital Univ. Munich

Adjusted fortification based on BUN enhances growth

Start standard fortification, 2x/wk blood urea nitrogen (BUN)

BUN mg/dL	BUN mmol/L	Adjustment
9-14	3.2-5	None
<9	<3.2	+1 Level
>14	>5	-1 Level

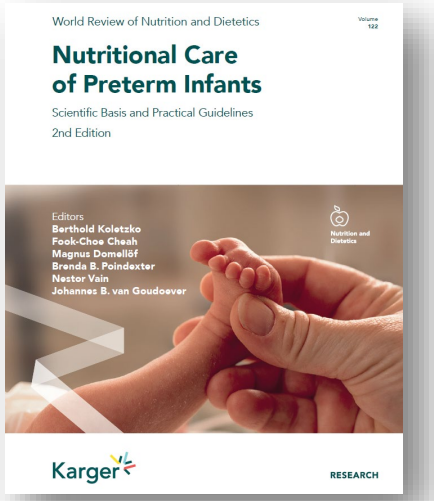
Fortification	g HMF/100 ml
3	6.25 + 0.8 prot
2	6.25 + 0.4 prot
1	6.25
0	5
-1	3.75
-2	2.5

Gain	Standard	Adjusted	P
Weight (g/d)	24.8	30.1	<0.01
Length (mm/d)	1.1	1.3	n.s.
HC (mm/d)	1.0	1.4	<0.05

Arslanoglu et al, J Perinatol 2006.

Dr. von Hauner Children's Hospital Univ. Munich

Fortification of human milk



- Always fortify human milk for very preterms/preterms <1800 g
- Start full strength fortification with 50–100 ml/kg&d of enteral feeding *(no strong evidence for optimal starting point)*
- Bovine protein multicomponent fortifiers recommended as standard
- No evidence for greater benefit of human milk-based fortifiers
- Aim at protein intakes >3g/kg/day
- Targeted/adjusted fortification recommended

If fortifiers are unavailable/unaffordable, formula powders have been used in LMIC

Should HM fortification continue after discharge?

Indications	*Human milk fed very preterm infants with* • Growth restriction at discharge (body weight <10th percentile or -1 SD, • and/or loss of >0.5 SD between birth and discharge, or poor postdischarge growth • Continuing medical problems, such as BPD • BUN levels <3.2 mmol/L (9 mg/dL) • Serum alkaline phosphatase >600 IU/L or phosphorus <1.6 mmol/L (5 mg/dL)
Modalities	*Addition of an MCF to expressed HM* • Mix expressed human milk with fortifier; combine with feeding unfortified human milk • About half of feeds as supplemented expressed breast milk *Alternatives* • Finger feeding of dissolved fortifier along with breastfeeding • Feed preterm formula alternating with breastfeeding
Monitoring	*Growth using appropriate growth chart* • Fenton growth chart until 50 weeks PCA • Then World Health Organization growth chart
Duration	Up to 40–52 weeks PCA, depending on growth

BPD, Bronchopulmonary dysplasia; BUN, blood urea nitrogen; PCA, postconceptional age; SD, standard deviation.

Picaud JC, Vicent M, Buffin R. Human Milk Forticificaiton for Preterm Infants: A Review. In: In: Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines. Koletzko B, et al. (eds): World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

Human Milk Fortification: Key Messages

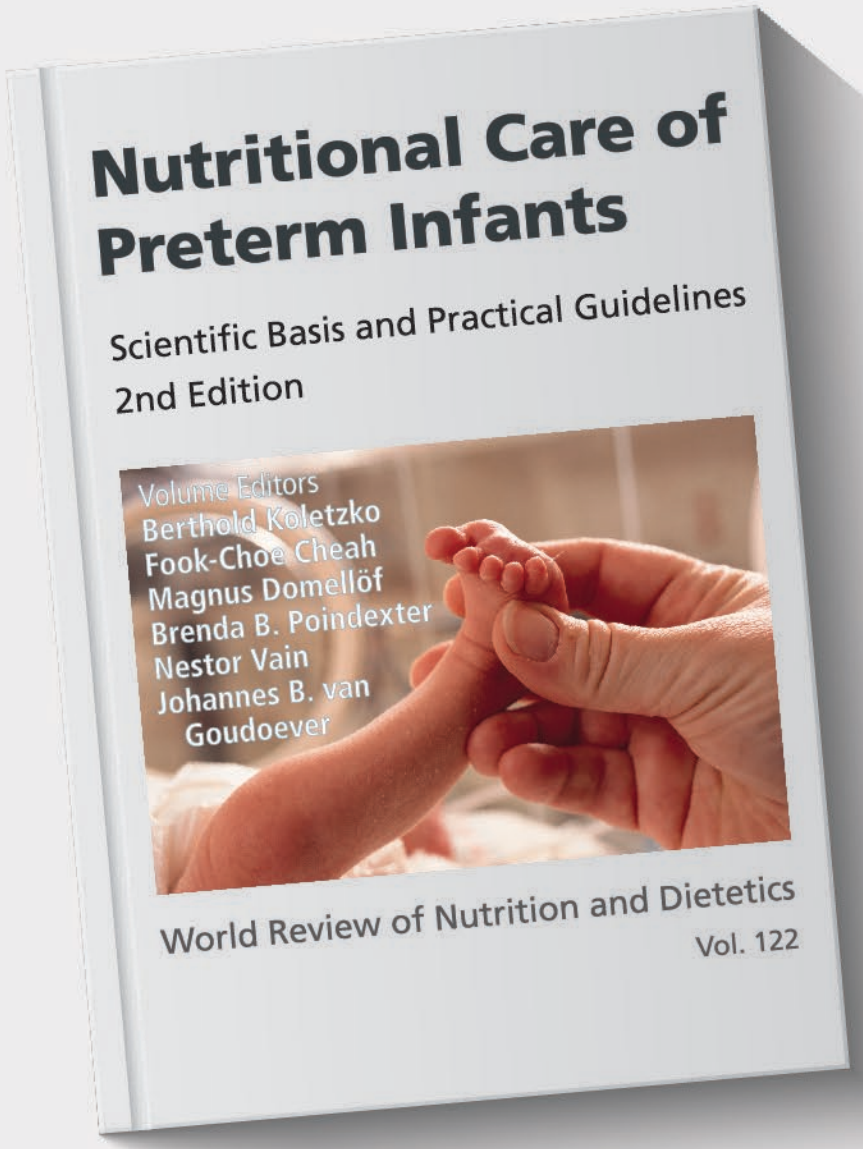
- Human milk with added fortifier is the preferred feeding for preterm infants
- Greater proportion of infants achieving adequate growth
- Delayed start increases risk of growth faltering
- Establish a written unit policy for promoting and supporting human milk feeding and for implementing human milk fortification for preterm infants
- Use targeted / adjusted fortification
- Continued fortification after hospital discharge may be beneficial, particularly for infants with growth faltering

Pichaud JC et al, in: Koletzko B et al, Nutritional Care of Preterm Infants, 2nd. ed. 2021, World Rev Nutr Diet 122.

Fortification of human milk: research needs

- Multi-nutrient human milk fortification was shown to improve in-hospital preterm growth, but data on later neurodevelopment are lacking and are needed
- More evidence needed on optimal timing of introducing fortifier
- Well designed, adequately powered controlled trials to compare use of fortifiers based on bovine vs. human milk are required
- Use of fortification with breastfeeding post-discharge should be further evaluated

Pichaud JC et al, in: Koletzko B et al, Nutritional Care of Preterm Infants, 2nd. ed. 2021, World Rev Nutr Diet 122.
Beggs MR et al, Acta Paediatr. 2022 Feb 10. doi: 10.1111/apa.16283.



Preterm Nutrition and Pulmonary Disease

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Fernando Moya, MD

Research Grant	*Mead Johnson Nutrition*
Speakers Bureau	*Mead Johnson Nutrition*
Speaker	*Chiesi Laboratories*

The grantor, Mead Johnson Nutrition, had no involvement in selecting faculty, editorial decisions, content or writing of this educational material.

Preterm Infants at Risk for Pulmonary Disease

- Preterm infants with IUGR at higher risk for RDS, chronic lung disease, and BPD-associated PAH [1]–[4]
- Birthweight Z-scores predictive of CLD risk; associated with growth restriction (defined as a BW Z-score < -1) [3]
- Excessive fetal growth can affect lung function
- VLBW infants in lower quartiles higher risk for neurodevelopmental and chronic pulmonary problems [4]
- Undernutrition affects lung function

CLD, chronic lung disease; IUGR, intrauterine growth restriction; PAH, pulmonary hypertension; RDS, respiratory distress syndrome; VLBW, very low birth weight.

1. Tyson JE, et al. *Pediatrics*. 1995;95:534–538; 2. Jensen EA, et al. *Arch Dis Child Fetal Neonatal Ed.* 2019; 104:F192–198; 3. Bose C, et al. *Pediatrics*. 2009;124:e450–458; 4. Bhat R, et al. *Pediatrics*. 2012; 129:e682–689.

Recommended Fluid Intakes

	Initial fluid intakes	Progressive fluid increases
Infants <1,750–2,000 g	60–80 mL/kg/day	max. 120–140 mL/kg/day by day 5–7 [a]
Results	May provide clinical advantages over starting with higher intakes and reaching total volumes above those values during first week after birth	

a. not for infants <750 g at birth (few from this cohort enrolled in trials)

- Neonatal lung function best preserved by avoiding free water overload
- Monitor weight, urine output, and electrolytes closely

Role of Nutrients in Neonatal Lung Function

Carbohydrates	• Glucose main source of carbohydrates in ELBW and VLBW • Excess may increase work of breathing in preterms with lung disease
Inositol	• Significant drop can result in severe RDS [1],[2]
Protein	• Prevents negative nitrogen balance • Stimulates protein accretion [3]
Triglycerides and fatty acids	• Critical for brain and retina development [4] • Important proinflammatory (n–6) or anti-inflammatory (n–3) roles • Acts as immune modulators [5] • DHA deficits → higher risk of BPD [6]
Calcium (Ca) Phosphorus (P) Potassium	• Critical for bone health & metabolic functions of cardiovascular and respiratory systems • Prevent or correct early in preterm infants with IUGR • Often decrease in preterm infants with IUGR (no ties shown between potassium and lung)

BPD, bronchopulmonary dysplasia; DHA, docosahexaenoic acid; IUGR, intrauterine growth restriction; RDS, respiratory distress syndrome.

1. Hallman M, et al. *Early Hum Dev.* 1985;10: 245–254; 2. Howlett A, et al. *Cochrane Database Syst Rev.* 2019;7:CD000366; 3. Poindexter B, et al. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. Elsevier; 2011:643–668; 4. Uauy R, et al. *Curr Opin Pediatr.* 2015;27:165–171; 5. Lapillonne A, et al. *J Pediatr.* 2013;162:S37–547; 6. Martin CR, et al. *J Pediatr.* 2011;159:743–749.

Role of Nutrients in Neonatal Lung Function *(continued)*

Vitamin A	• Deficiency → decreased lung growth and repair • Lower plasma retinol levels → increased risk long-term respiratory morbidity [1]
Vitamin D	• Linked to lung maturation (pneumocyte differentiation and surfactant production) [2]–[4] • Early supplementation safe; may prevent respiratory morbidity
Vitamin E	• Antioxidant properties protect cell membranes
Selenium (Se)	• Critical to generate antioxidant enzymes [5],[6] • Supplementation not associated with reduced risk of CLD [7]
Zinc (Zn)	• Important micronutrient for growth and development

CLD, chronic lung disease.

1. Spears K, et al. *Am J Clin Nutr.* 2004; 80:1589–1594; 2. Zosky GR, et al. *Ann Am Thorac Soc.* 2014;11: 571–577; 3. Nguyen TM, et al. *Am J Physiol.* 1996;271(3 Pt 1):L392–399; 4. Phokela SS, et al. *Am J Physiol Lung Cell Mol Physiol.* 2005;289:L617–626; 5. Tindell R, et al. *J Perinatol.* 2018; 38:197–202; 6. Darlow BA, et al. *Cochrane Database Syst Rev.* 2003;4:CD003312.

Postnatal Supplementation With DHA

Lipid emulsions with marine oils

- Good source of DHA and LC-PUFAs

Preterm infants prone to DHA deficiency

- Without external sources of n–3 PUFAs, preterm infants can develop DHA deficiency [1]
- DHA deficiency associated with higher risk of BPD [2]

Maternal supplementation of DHA

- DHA-enriched breast milk shown to lower risk of BPD among infants with birth weight <1250 g. [3],[4]

BPD, bronchopulmonary dysplasia; DHA, docosahexaenoic acid; LC-PUFAs, long-chain polyunsaturated fatty acids.

1. Robinson DT, et al. *J Pediatr.* 2013;162:56–61.
2. Martin CR, et al. *J Pediatr.* 2011;159:743–749.
3. Manley BJ, et al. *Pediatrics.* 2011;128;e71–77.
4. Joss-Moore L, et al. *Early Hum Dev.* 2010;86:785–791.

DHA and BPD in Infants <29 Weeks' Gestation
(DHA at 60 mg/kg/d)

Outcome	DHA Group (N = 592)	Control Group (N = 613)	Adjusted Effect (95% CI)	Adjusted *P* Value
Physiological BPD: primary outcome—no. (%)	291 (49.1)	269 (43.9)	1.13 (1.02–1.25)	0.02
Physiological BPD or death before 36 wk of postmenstrual age—no./total no. (%)	330/631 (52.3)	298/642 (46.4)	1.11 (1.00–1.23)	0.045
Clinical BPD—no./total no. (%)	315/592 (53.2)	304/612 (49.7)	1.09 (1.00–1.18)	0.06
Severity of BPD				
Mild—no. (%)	80 (13.5)	108 (17.6)	0.76 (0.58–0.99)	0.04
Moderate—no. (%)	65 (11.0)	50 (8.1)	1.35 (0.95–1.92)	0.10
Severe—no./total no. (%)	202/592 (34.1)	194/612 (31.7)	1.07 (0.93–1.22)	0.36
Surfactant use—no./total no. (%)	533/631(84.5)	516/642 (80.4)	1.05 (1.00–1.10)	0.06
Days of respiratory support	41.5±28.7	40.4±27.7	1.02 (0.94–1.10)	0.63
Postnatal glucocorticoids—no./total no. (%)	128/604 (21.2)	132/622(21.2)	0.98 (0.80–1.19)	0.81

	DHA	Placebo
DHA at randomization	2.7±0.9	2.7±0.9
DHA at 36 weeks	3.9±0.7	2.5±0.6

% of whole blood total FA

Collins CT, et al. *N Engl J Med.* 2017;376(13):1245-1255. Top table adapted from Table 2.

Maternal DHA Supplementation to Prevent BPD in Breast-Fed Preterm Infants

- Blind RCT of maternal supplementation with 1.2 g/d of DHA/placebo
- Lactating women who delivered < 29 weeks were eligible
- DHA: 232 mothers (273 infants), Placebo: 229 mothers (255 infants)
- Primary endpoint BPD-free survival at 36 wks PMA
- Enrollment was stopped early due to concern for harm

Outcome	DHA (N= 232)	Placebo (N= 229)	RR (95% CI)	*P*
GA at birth (wk + SD)	26.7 + 1.5	26.4 + 1.6	-	-
BW at birth (Kg + SD)	0.89 + 0.24	0.89 + 0.23	-	-
DHA % of total FA in BM (mean, 95% CI)	0.95 (0.89–1.01)	0.34 (0.31–0.37)	-	<0.001
BPD free survival at 36 wk PMA	54.9%	61.6%	0.91 (0.80–1.04)	0.18
Death before 36 wk PMA	6.0%	10.2%	0.61 (0.33–1.13)	0.12
Severe IVH (grade 3 or 4)	7.7%	16.1%	0.48 (0.29–0.80)	0.005
ROP needing treatment	8.0%	8.4%	0.97 (0.52–1.81)	0.93
NEC > stage 2	5.4%	3.0%	2.02 (0.79–5.18)	0.14

Marc I, et al. *JAMA.* 2020;324(2):157-167.

Systematic Review of Vitamin A to Prevent Morbidity and Mortality in VLBW infants

Vitamin A may result in a modest reduction of risk of chronic lung disease

Outcome [1]	**Number of studies**	**Number of participants**	**Risk ratio (95% CI)**
Neonatal death	6	1,165	0.86 (0.66–1.11)
Death before 36 weeks' PMA	4	1,089	1.00 (0.77–1.29)
Chronic lung disease (O_2 use at 1 month in survivors)	7	1,070	0.93 (0.86–1.01)
Chronic lung disease (O_2 use at 36 weeks' PMA in survivors)	5	986	0.87 (0.77–0.99)
Death or chronic lung disease (O_2 at 36 weeks' PMA)	4	1,089	0.92 (0.84–1.01)

PMA, postmenstrual age.

1. Darlow et al. *Cochrane Database Syst Rev*. 2016;8:CD000501.
2. Moya F, Salas AA. Preterm nutrition and pulmonary disease. In: Koletzko B, et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. World Rev Nutr Diet. Basel, Karger, 2021, vol 122.

Postnatal Supplementation With Vitamin A

Study	Cohort preterms	Study design	Results
Tyson et al 1999	n=807; mean 770 g VA grp; 769 g ctrl grp; GA 26.8 and 26.7 weeks	5,000 IU, intramuscular admin. few days after birth 3x per week for 4 weeks	• reduced risk of BPD by ~7%
Araki et al 2018 systematic review, meta-analysis	ELBW infants; n=841	Intramuscular admin. in 3 studies; oral in 1 study	• modest reduction of O_2 dependency in 36 wks' survivors (RR 0.88, 95% CI 0.77–0.99) • Length of hospital stay reduced in Vit A group
Basu et al 2019	VLBW infants n=196	10,000 IU, enterally alternate days, for 28 days	• reduction of all-cause mortality and O_2 requirement for 28 days (RR 0.44, 95% CI 0.23–0.84) • fewer cases of late-onset sepsis • BPD (O_2 needed at 36 wks) in a small proportion in both grps
Mazumder et al 2015	n= 44,984 to receive vitamin A (22,493) placebo (22,491)	50,000 IU vitamin A within first 72 h of life	• modest reduction in mortality btwn supplementation and 6 m of age, generally safe and well tolerated

ELBW, extremely low birth weight; GA, gestational age; VLBW, very low birth weight.

1. Tyson JE, et al. *N Engl J Med.* 1999; 340:1962–1968.
2. Araki S, et al. *PLOS One.* 2018;13:e0207730.
3. Basu S, et al. *Eur J Pediatr.* 2019;178: 1255–1265.
4. Mazumder S, et al. *Lancet.* 2015;385(9975):1333-1342.

Postnatal Supplementation With Zinc

- Preterm birth is risk factor for Zn deficiency (<55mcg/dL); 60% of Zn accretion occurs in 3rd trimester [1]
- Single-center, retrospective analysis showed initiating Zn at avg of 33 wks PMA in ELBW infants with poor weight gain (N=52) → increased weight gain and linear growth. [1]
- Current study to determine whether enteral Zn supplementation leads to improved growth in infants at risk for BPD [2]

BPD, bronchopulmonary dysplasia; PMA, postmenstrual age; Zn, zinc.

1. Shaikhkhalil AK, et al. *J Pediatr Gastroenterol Nutr.* 2014;58:183–187.
2. ClinicalTrials.gov. NCT03532555. Recruiting.

Practical Application

- Avoid high glucose infusion rates >10–12 mg/kg/min for infants who have restrictions to eliminate CO_2 due to lung disease.
- Follow serum phosphorus (P) early on, especially in growth restricted PT babies. A low serum P is associated with need for longer mechanical ventilation and higher risk for BPD.
- Consider vitamin A supplementation in management of ELBW infants at high risk for chronic lung disease given its low cost and margin of safety in doses studied.

ELBW, extremely low birth weight.

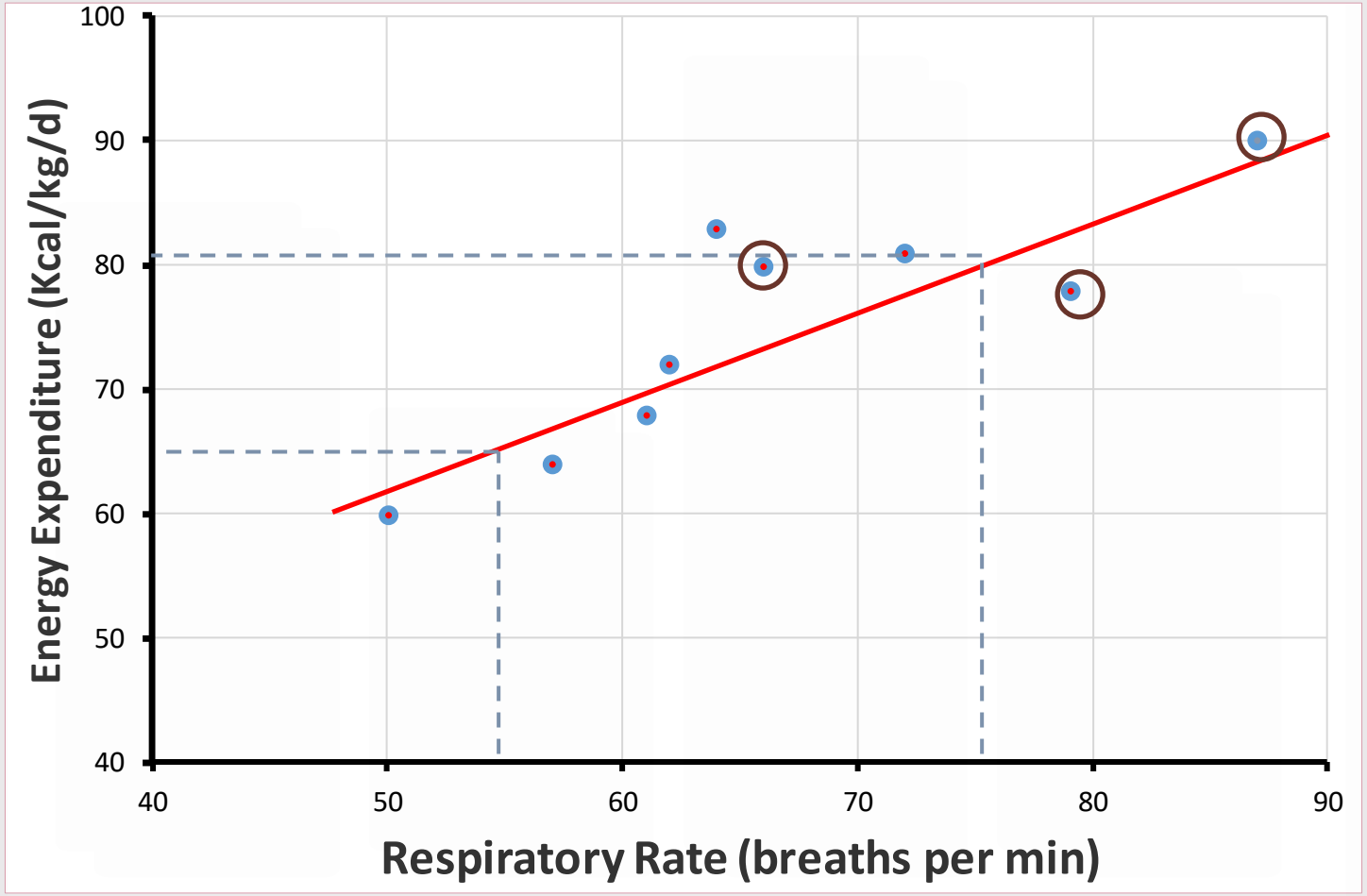
Practical Application

- For preterm infants on respiratory support who frequently develop abdominal distention consider:
  - Slowing feeds:
    - » Lung compliance and resistance are lower during continuous feeds compared with bolus [1]
  - Positioning:
    - » Lower energy expenditure (3 kcal/kg/day) in prone position [2]
  - However, babies with severe BPD are at greater risk for desaturation episodes with transpyloric feedings [3]
  - Providing breast milk via continuous feeds may lead to up to 50% loss of fat, hence energy [4]

1. Blondheim O, et al. *J Pediatr.* 1993;122(5 Pt 1):751-755.
2. Masterson J, et al. *Pediatrics.* 1987;80(5):689-692.
3. Jensen EA, et al. *Arch Dis Child Fetal Neonatal Ed.* 2020;105(4):399-404.
4. Vieira AA, et al. *Early Hum Dev.* 2011;87(8):577-580.

Practical Application

For infants with increased work of breathing and slower growth, consider adding fat as a source of energy (MCT Oil).



Adapted from Figure 1. de Meer K, et al. *Eur J Pediatr.* 1997;156(4):299-304.

Key Takeaways in Preterm Infants

- Avoid high glucose infusion rates over 10–12 mg/kg/min among infants who have restrictions to eliminate CO_2 due to lung disease.

- Start parenteral nutrition with amino acids soon after birth. Advance to 3.5 g/kg/day within the first days of life, balancing with increasing energy intake. Consider using intravenous lipid solutions that provide DHA.

Research Priorities

- **Large studies of maternal and early neonatal supplementation of DHA/ARA to reduce the risk of BPD and with focus on pulmonary function**
- **Large human studies to determine zinc serum levels in infants with poor growth, specifically with BPD, and potentially supplement those who are deficient**