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Intravenous Nutrition for Preterm Infants

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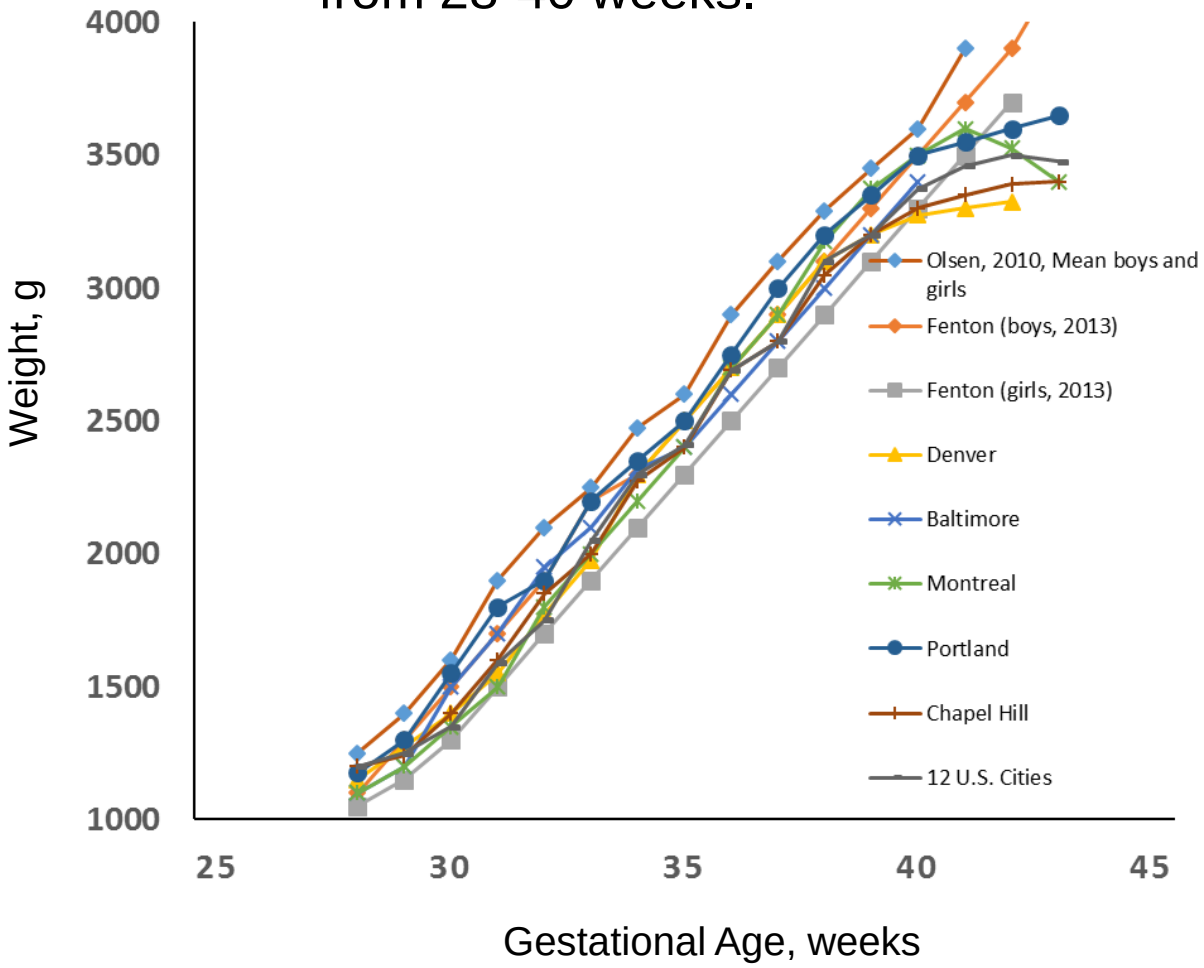
What is the normal fetal growth rate?

Regardless of the growth curve, the normal *average* human fetal growth rate is **~17 g/kg/day** from 28-40 weeks.



Birth weights by gestational age

From six sources adapted from Naeye R, Dixon J. Pediatr Res 1978;12:987-991;

Fenton TR, Kim JH. BMC Pediatr 2003;13:59;

Olsen IE, et al. Pediatrics 2010; 125:e214-e224.

If the goal for nutrition of the preterm infant is to

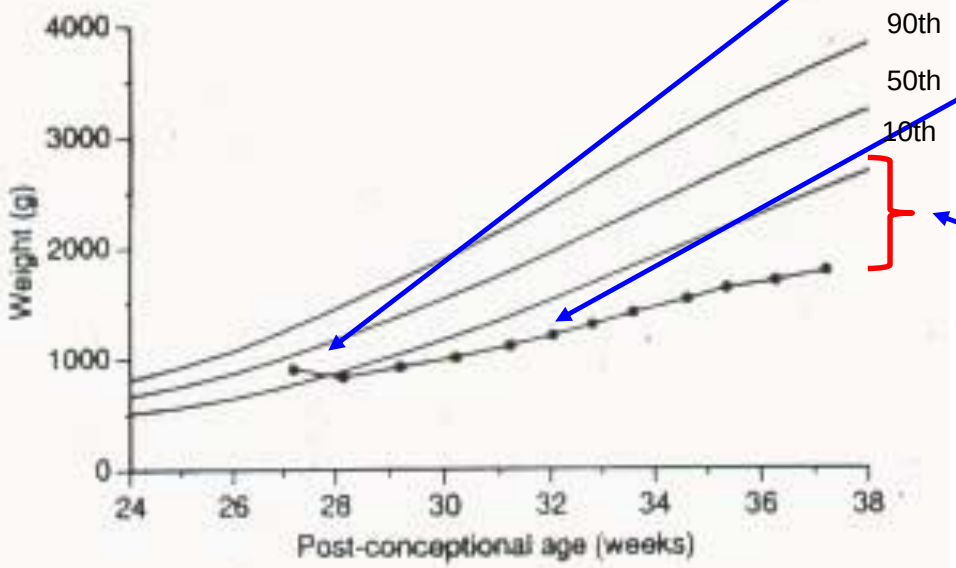
"Achieve postnatal growth rate approximating that of the normal fetus of the same gestational age",

AAP, 1998

and we have a reasonable idea of what that growth rate should be,

How are we doing?

Not that well.



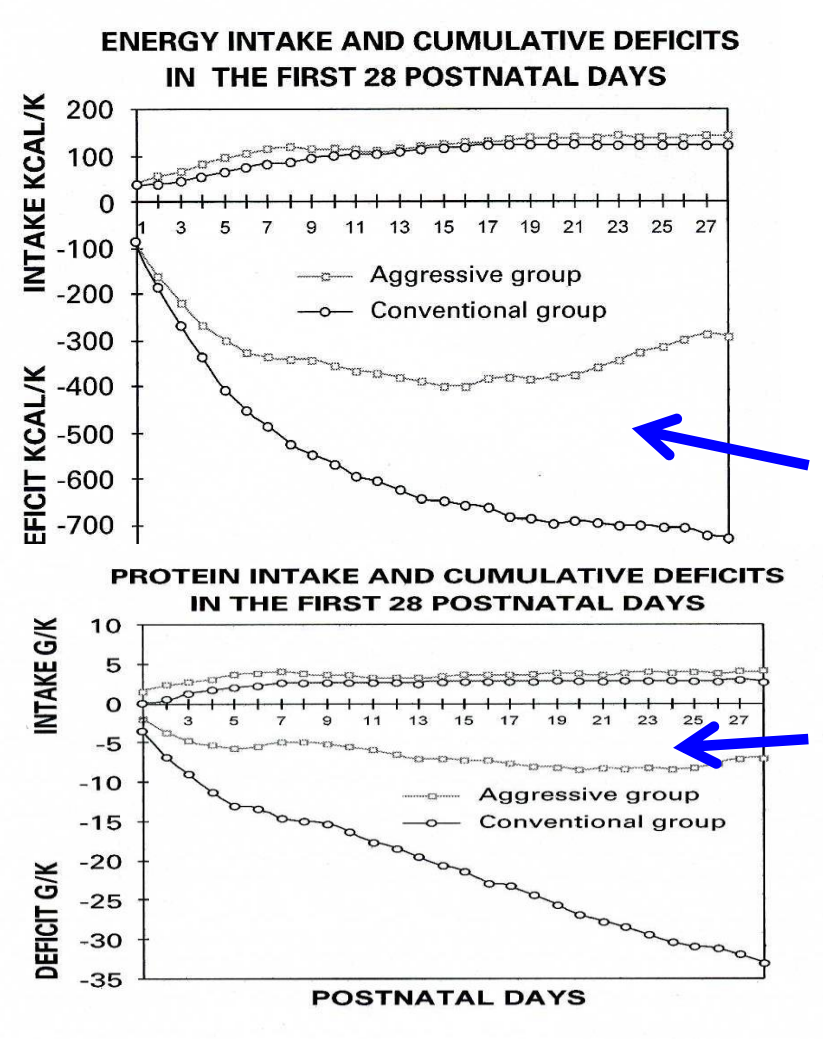
Carlson & Ziegler, J Perinatol 1988.
Average weight of infants: -•-
Curves represent 10th, 50th, and 90th percentiles of intrauterine weight (Arbuckle et al., 1993).

Most preterm infants fail to grow after birth for many days,

they don't keep up with intra uterine growth,

and thus they end up growth restricted by term.

This problem has not improved over the past 65+ years! WHY?



A principal reason—
inadequate nutrition

as evidenced by cumulative deficits in

energy

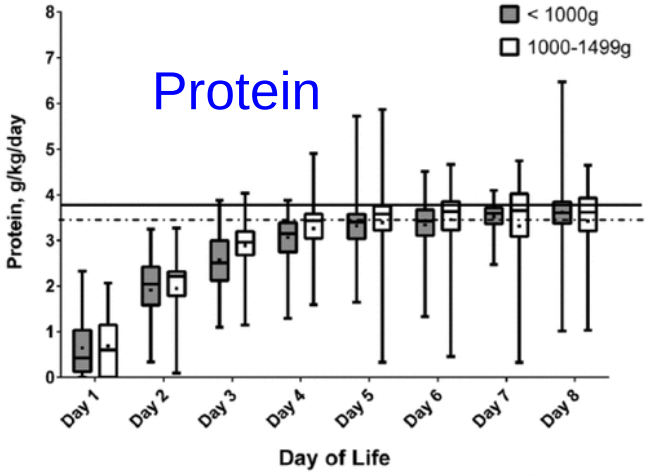
and

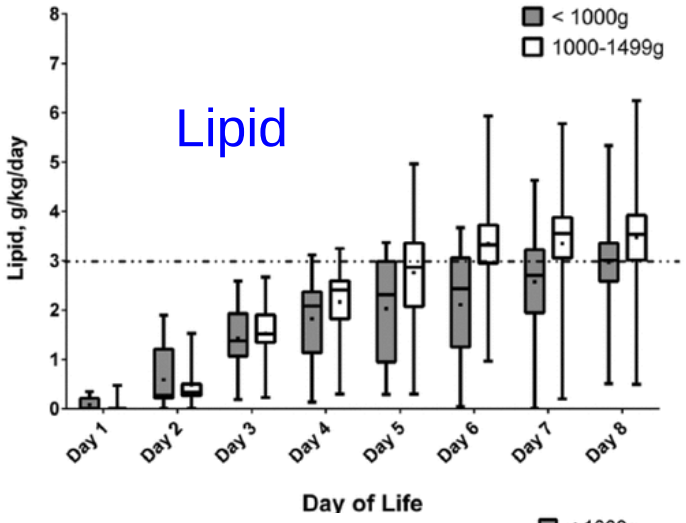
protein

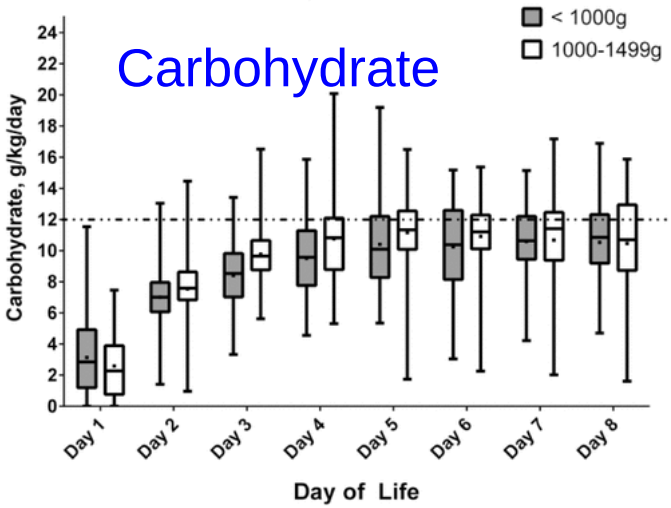
even with “aggressive” feeding (-□-).

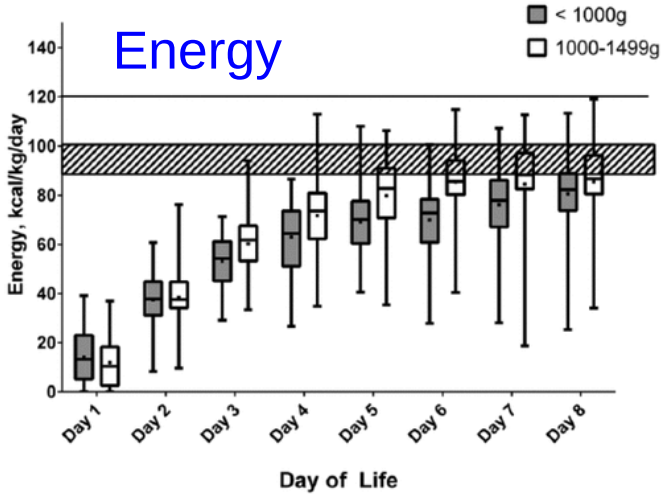
Dinerstein et al, J Perinatol 26:436-442, 2006

And still true today, among VLBW and LBW preterm infants—









Nutrient goals not achieved until day 5-8.

Ng DVY, et al. How Close Are We to Achieving Energy and Nutrient Goals for Very Low Birth Weight Infants in the First Week? JPEN 2017;41:500-506.

Intravenous Nutrition: General Principles

1. Metabolic and thus nutritional requirements do not stop with birth; this includes protein accretion.

2. The smaller the infant, the less body stores (protein, fat, glycogen) are available to provide nutrients for metabolic needs.

3. Intravenous feeding is always indicated when normal metabolic needs are not met by normal enteral feeding.

4. The metabolic and thus nutrient requirements of the newborn are equal to or greater than those of the fetus of the same gestational age.

5. It is reasonable, therefore, to provide the preterm infant with at least what the fetus of the same gestational age receives for nutrition to maintain normal metabolism.

“Nutrients” for Preterm Infants

- **Glucose**
- **Lipids**
- **Amino Acids**
- **Insulin**

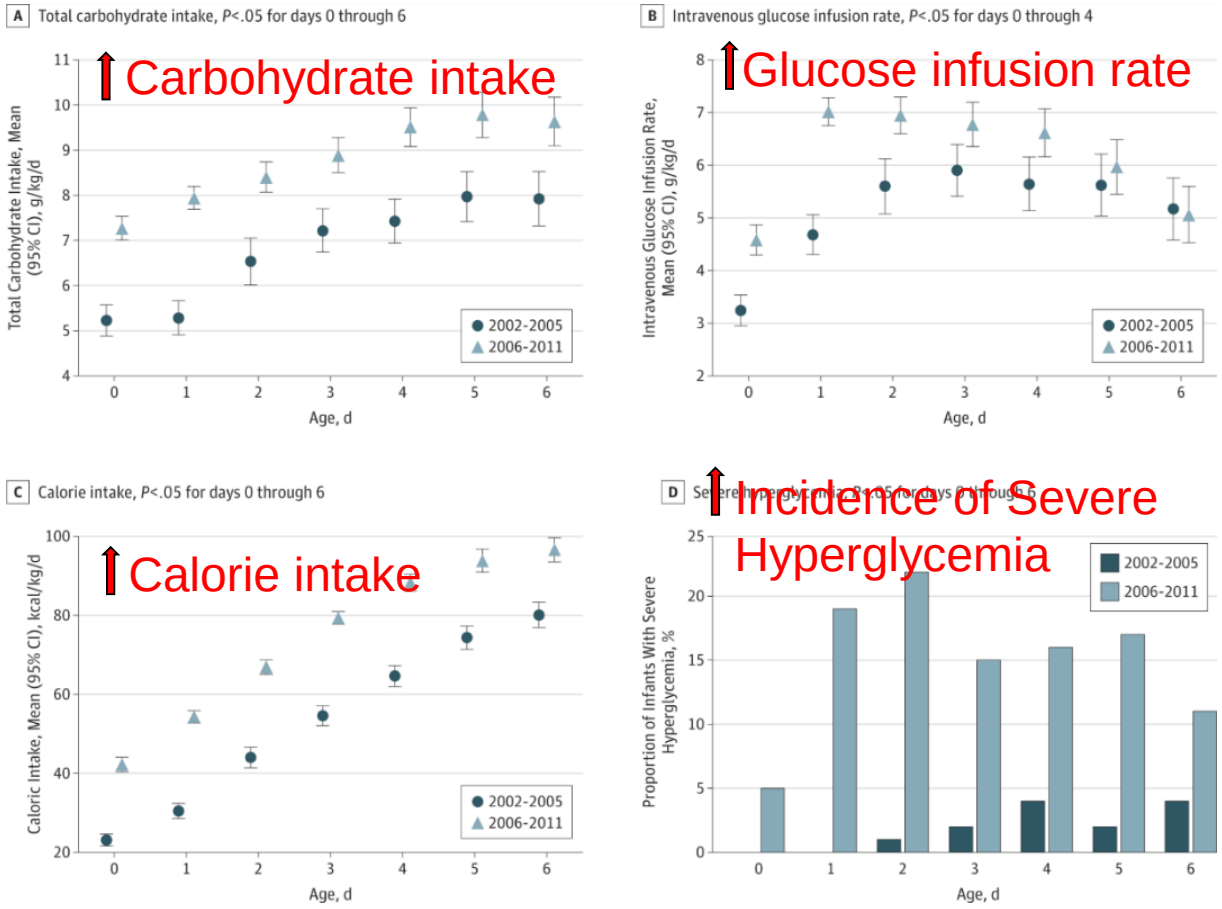
Reducing fetal glucose supply enough to decrease fetal glucose and insulin concentrations restricts fetal growth—
Some energy is necessary for protein synthesis and balance.

	Control	Chronic Hypoglycemia	
Fetal weight (kg)	3.58 (0.2)	2.76 (0.2)	- 24%
Fetal Glucose Uptake (mg/min/kg)	4.8 (0.4)	l.2 (0.2)	- 75%
Glucose (mg/dL)	18.1 (0.9)	9.8 (0.8)	- 46%
Insulin (uU/mL)	11 (1)	4 (1)	- 64%

Data from Carver TD, et al. *Pediatr Res.* 1995;38:754-762.

But this is very uncommon in preterm infants, who more often are infused with more glucose than they can use.

And the excess dextrose infusion produces **HYPERGLYCEMIA**, which has become almost universal in recent years (2006-2011▲ vs. 2002-2005 ●).



Severe hyperglycemia:

2 or more consecutive values of >216 mg/dL (>12 mM/L) at least 3 hrs apart.

Highly (0.001) associated (marker or cause??) with death risk.

Stensvold HJ, et al., JAMA Pediatr. Published online, September 08, 2015.1-8

How much Glucose?

Neonatal Glucose Production and Utilization Rates

Preterm 28 week

Production: 2-3 mg/min/kg

Utilization: 6-8 mg/min/kg up to 10 mg/min/kg.

mostly for the brain.

Start 4-5 mg/min/kg, adjust frequently to keep glucose >3 mmol/L, <6 mmol/L

Term

Production: 3-5 mg/min/kg

Utilization: 3-7 mg/min/kg up to 10 mg/min/kg.

still mostly for the brain, but weight-specific rate ”diluted” by organs that don’t use as much glucose as the brain: bone, fat, muscle.

Start 3-4 mg/min/kg, adjust frequently to keep glucose >3 mmol/L, <6 mmol/L

“Nutrients” for Preterm Infants

- Glucose
- **Lipids**
- Amino Acids
- Insulin

Lipid

- **There are sufficient essential fatty acids in IV lipid emulsions at 1.0 g/kg/day.**

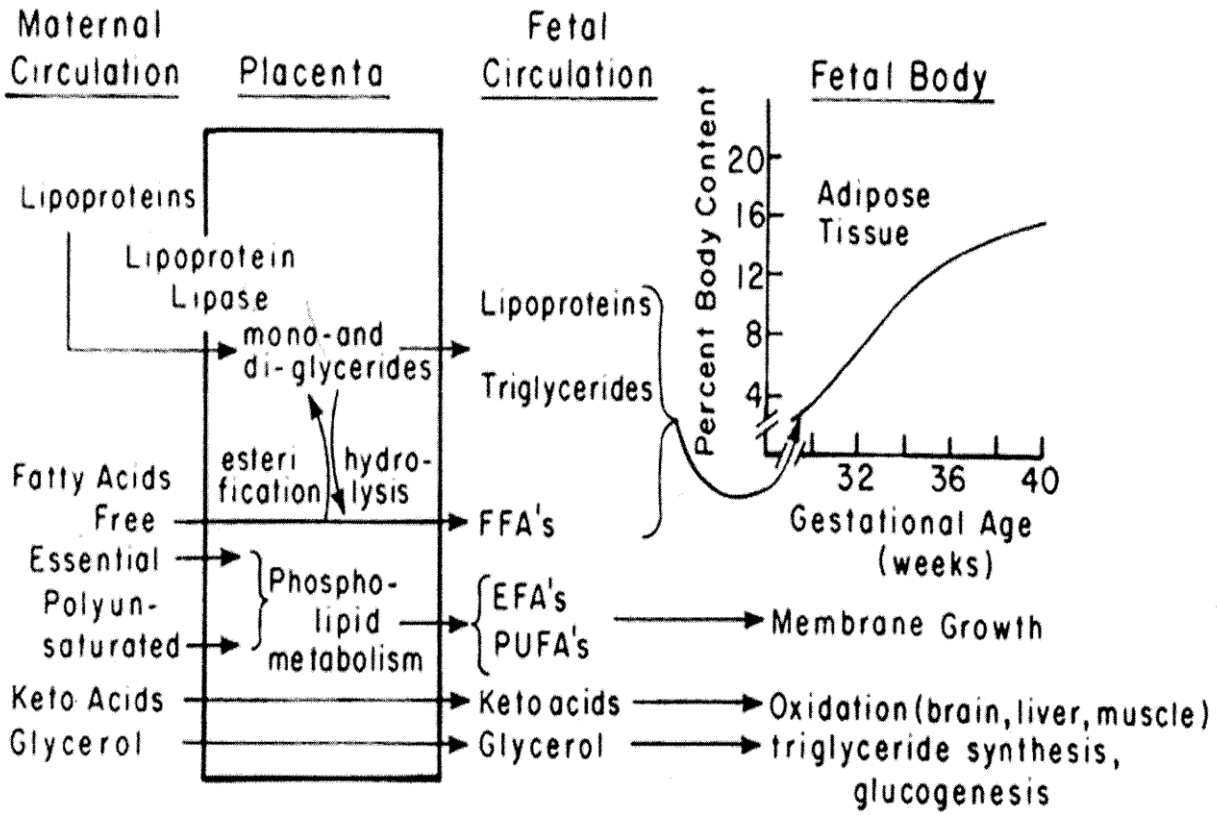
With lower energy, all fatty acids, essential or otherwise, are oxidized and will produce EFA deficiency.

- **Thus, lower limit should be 1.0 g/kg/day, but only for 2-3 days.**

Extremely preterm infants often are slow to clear plasma lipids due to:

- Maturational deficiency of lipases (inversely related to GA)
  - Rx—enteral feeding
- Low levels of carnitine palmitoyltransferase (CPT) and chronically reduced carnitine intakes >2 weeks after birth with prolonged IV nutrition.
  - Rx—even in preterm infants, and even right after birth, carnitine in mother's milk (and preterm formulas) promotes lipid oxidation—enteral feeding.
- Competition of FFA oxidation from hyperglycemia
  - Rx—reduce IV dextrose, advance enteral feeding

What about the quality of lipids supplied to the fetus and their plasma concentrations in the fetus?



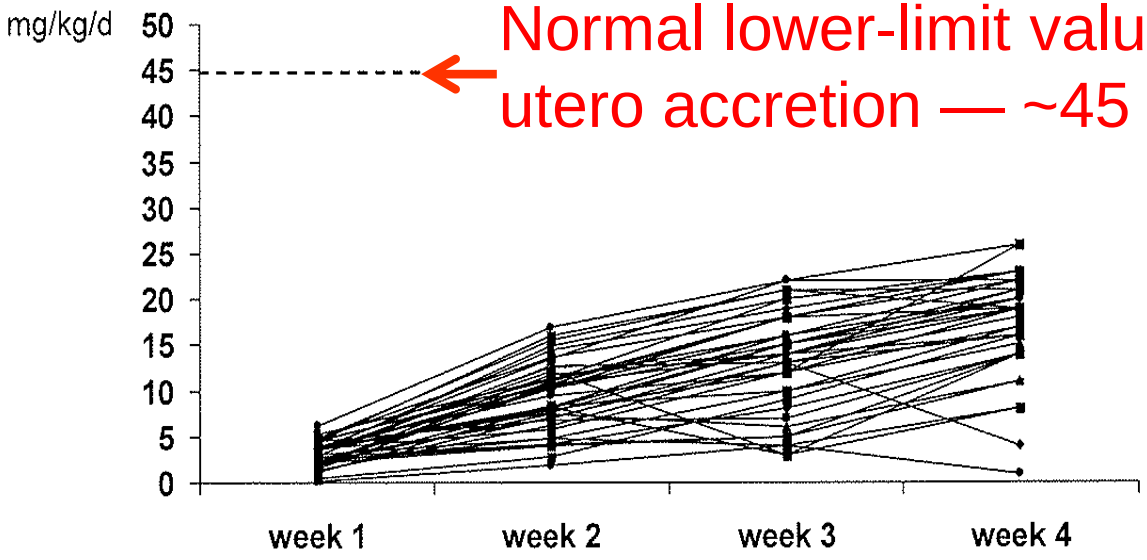
The placenta produces a unique mix and concentration of lipids in fetal plasma.

What is the importance of this for normal fetal development?

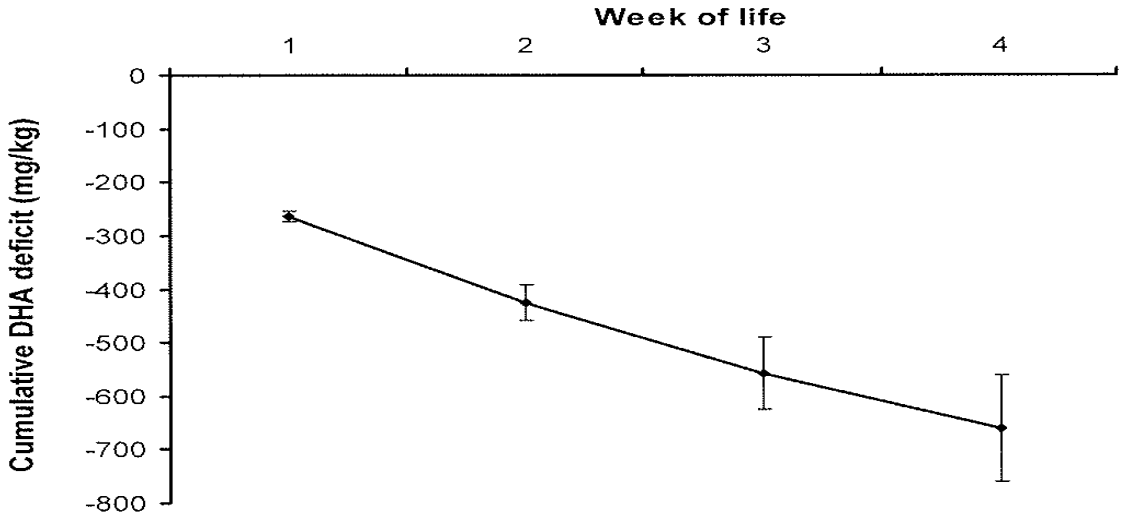
Should it be mimicked in preterm infants?

Fetal white adipose tissue accumulation during last trimester—n-3 accretion ≈ 45-65 mg/day (mostly 22:6n-3)

At 3.7g fat/dL human milk with 0.2-0.4% fatty acids as 22:6n-3, a 1 kg preterm infant fed at full enteral feeds of 180 mL/day (!!) would get only 13-25 mg 22:6n-3/day, clearly below normal *in utero* accretion rates.



Normal lower-limit value for in utero accretion — ~45 mg/kg/day



Postnatal DHA deficiency is an inevitable consequence of current recommendations and practices for feeding milk, milk supplements, and formulas in preterm infants.

Lapillonne et al, Neonatology, 2011.

Benefit of DHA supplementation?

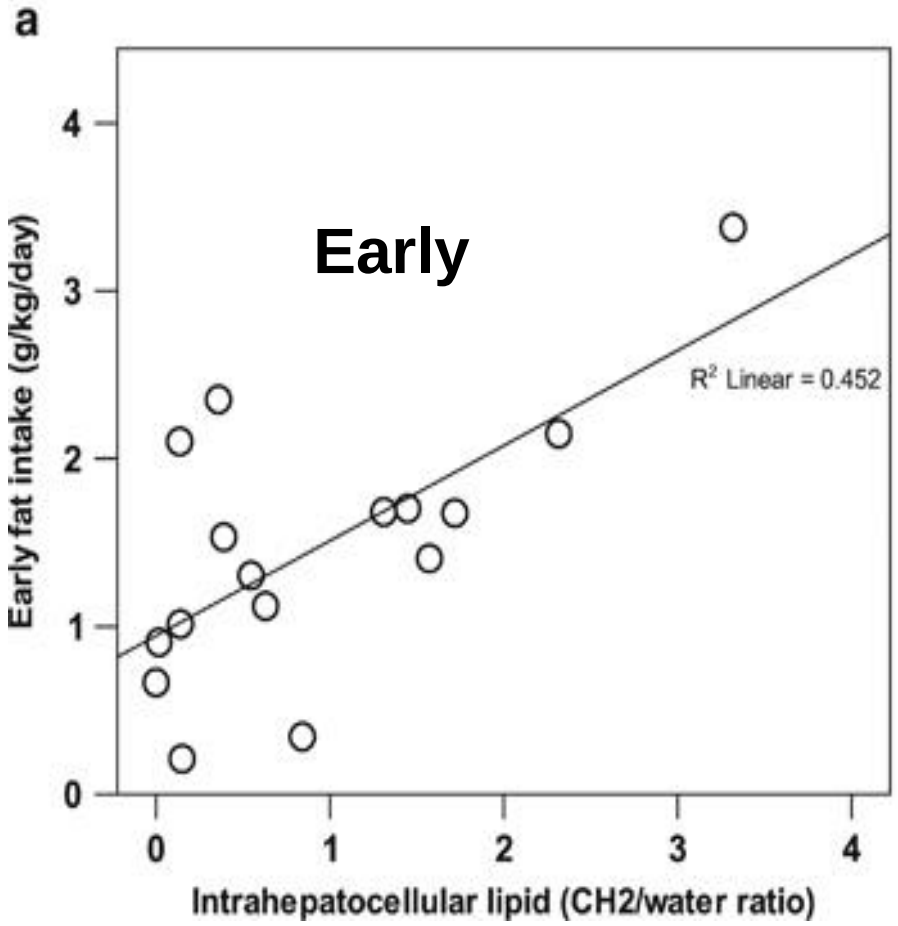
Preterm infants fed increased 22:6n-3 (Docosahexaenoic acid) have:

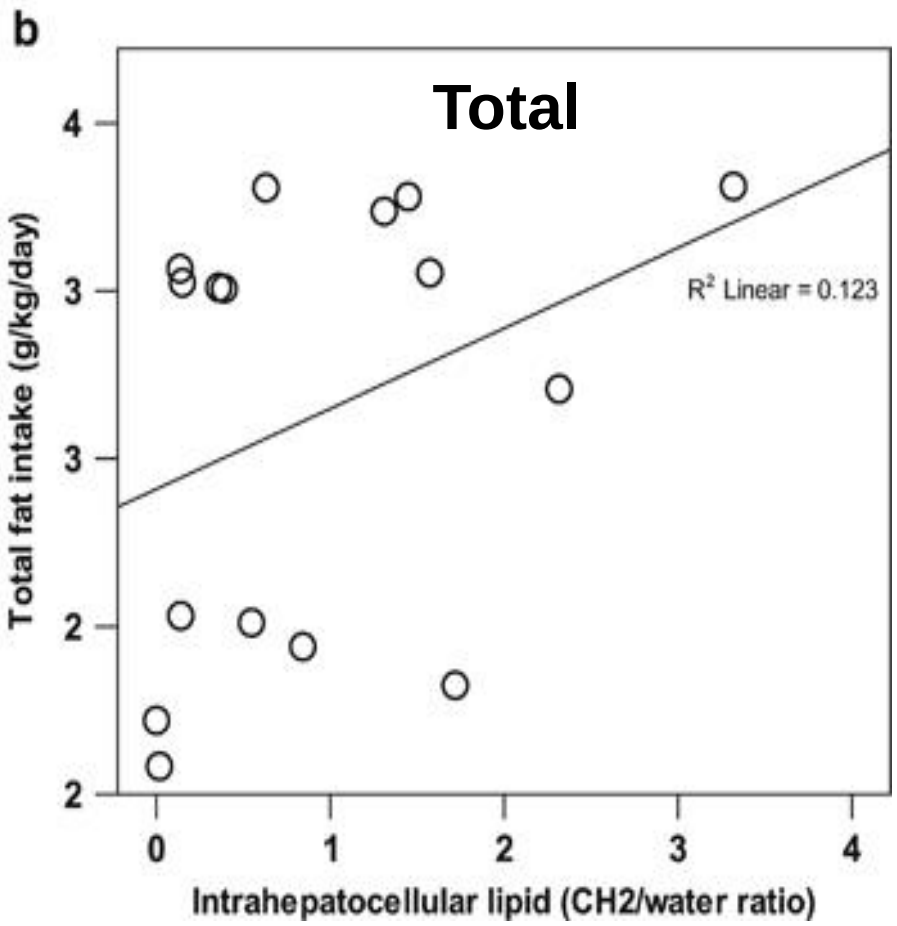
- **higher visual acuity, particularly at 2 and 4 months.**
- **improved Bayley mental development and MacArthur Communicative inventories at 12 months.**
- **But—longer term studies do not show a clear benefit.**

Thus--

- **The current diet for preterm infants is deficient in this essential fatty acid.**
- **The long term significance of this deficiency is not known,**
- **or how these infants would develop if fed to sufficiency!**

But, excess lipid infusion also has adverse consequences--

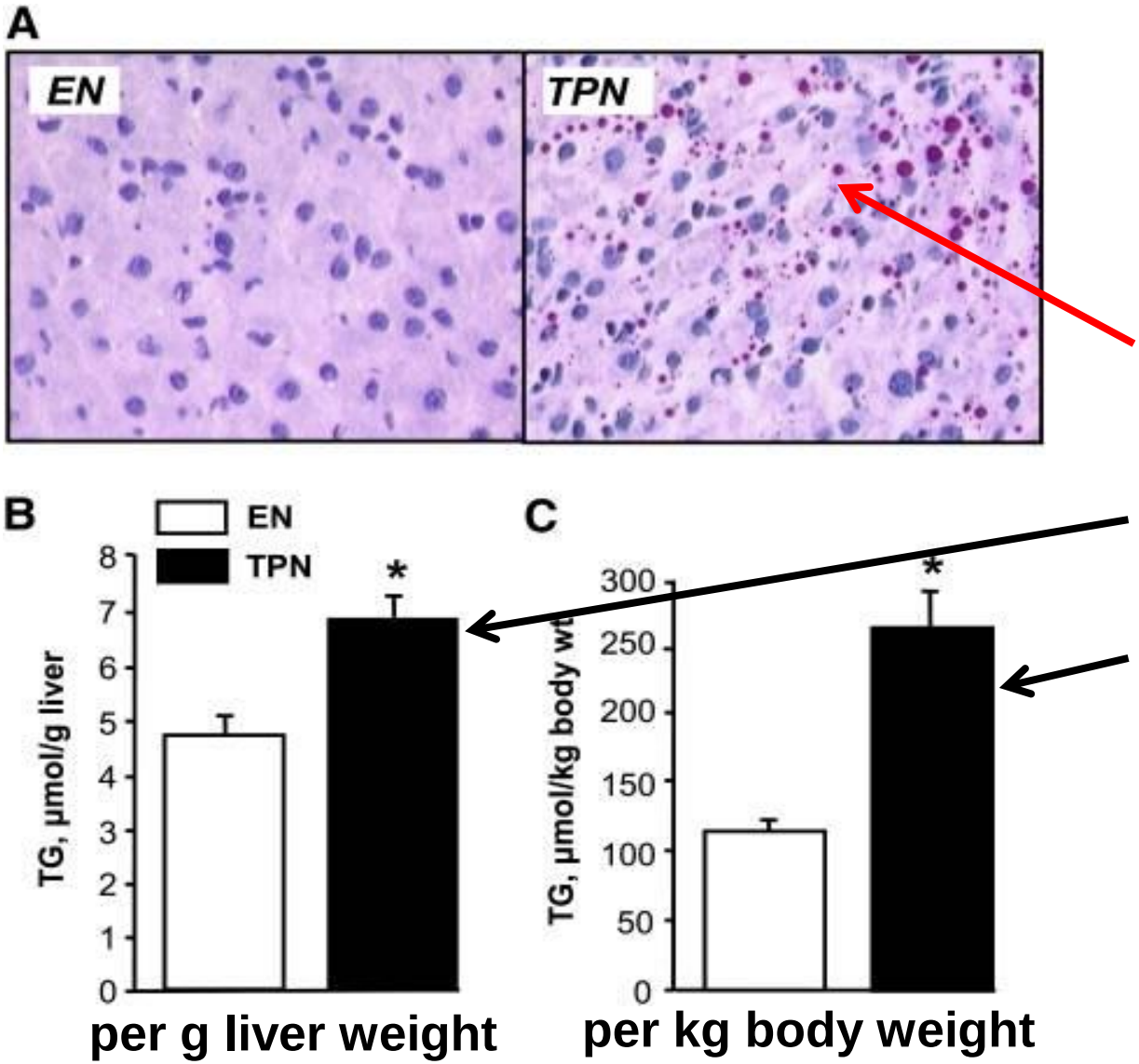




Relationship between **Intrahepatocellular lipid content** and (a) early fat intake and (b) total fat intake in preterm infants.

V Vasu, et al. Early nutritional determinants of intrahepatocellular lipid deposition in preterm infants at term age. Int J Obes (Lond). 2013; 37:500-4.

Parenteral Nutrition Associated Liver Disease (hepatic steatosis): from excess glucose? from lipids? something else?



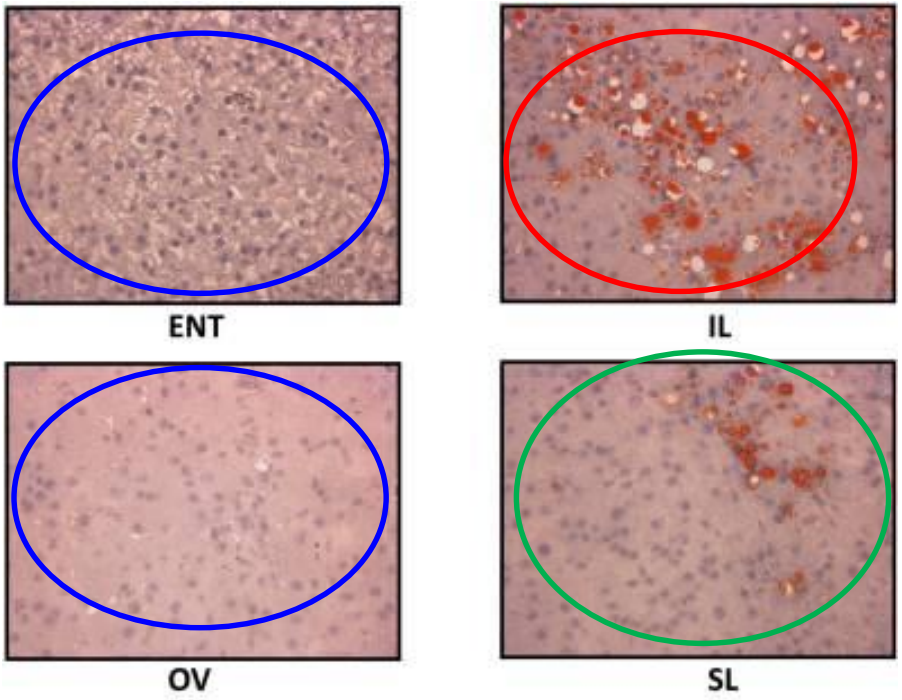
Hepatic lipid content in neonatal pigs fed EN or TPN for 17 d. (*A*) Oil Red O-stained liver sections showing **lipid droplets (red)** in livers from EN or TPN pigs after 17 d. (*B*) **Increased hepatic triglyceride (TG) content** per g tissue and (*C*) per kg body weight (BW) in neonatal pigs fed EN or TPN for 17 d.

Stoll B, et al. J Nutr 2010;140:2193-2200.

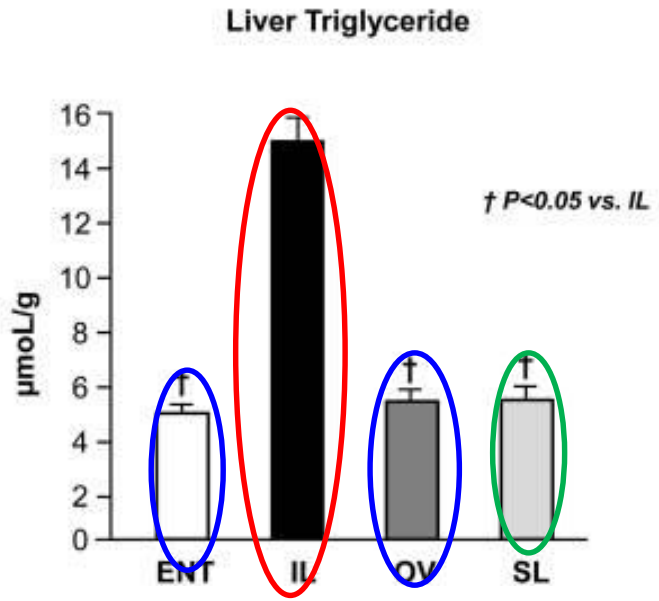
Recent evidence for reduced PNALD with increased anti-inflammatory DHA intake in lipid emulsions containing Fish Oil and reduced inflammatory phytosterols

	Intralipid	Omegaven	Somoflipid	Lipoplus
Oil	soybean 100%	**Fish 100%**	Soy 30 Olive 25% Coconut 30% **Fish 15%**	Soy 40% Coconut 50% **Fish 10%**
Linoleic	**44 – 62**	**0.1 - 0.7**	**22**	**24.5**
Linolenic	4 – 11	0.2	2	3.5
Palmitic	7 – 14	0.25 - 1.0	10	6
Oleic	19 – 30	0.6 - 1.3	31	8
DHA	**0**	**1.4 - 3.1**	**2**	**2.5**
Alpha-Tocopherol	38 mg/dL	150-296 mg/dL	48	?
Phytosterols	**343 mg/L**	**0**	**48**	**?**

Kasmi E, et al. Phytosterols promote liver injury and Kupffer cell activation in parenteral nutrition-associated liver disease. Sci Transl Med 2013;5:206.



TPN-fed pigs given soybean oil (IL) developed cholestasis and steatosis that was prevented with both Omegavin (OV) and Smoflipid (SL) emulsions (compared with enterally-fed pigs). Due to the presence of phytosterols in the SL emulsion, the differences in cholestasis and liver injury among lipid emulsion groups in vivo were weakly correlated with plasma and hepatic phytosterol content.



Vlaardingerbroek H, et al.
J Lipid Res 2014;55:466-477.

Energy

Unfounded concern that higher intake rates of amino acids/protein won't produce more growth unless higher calorie intakes also are provided.

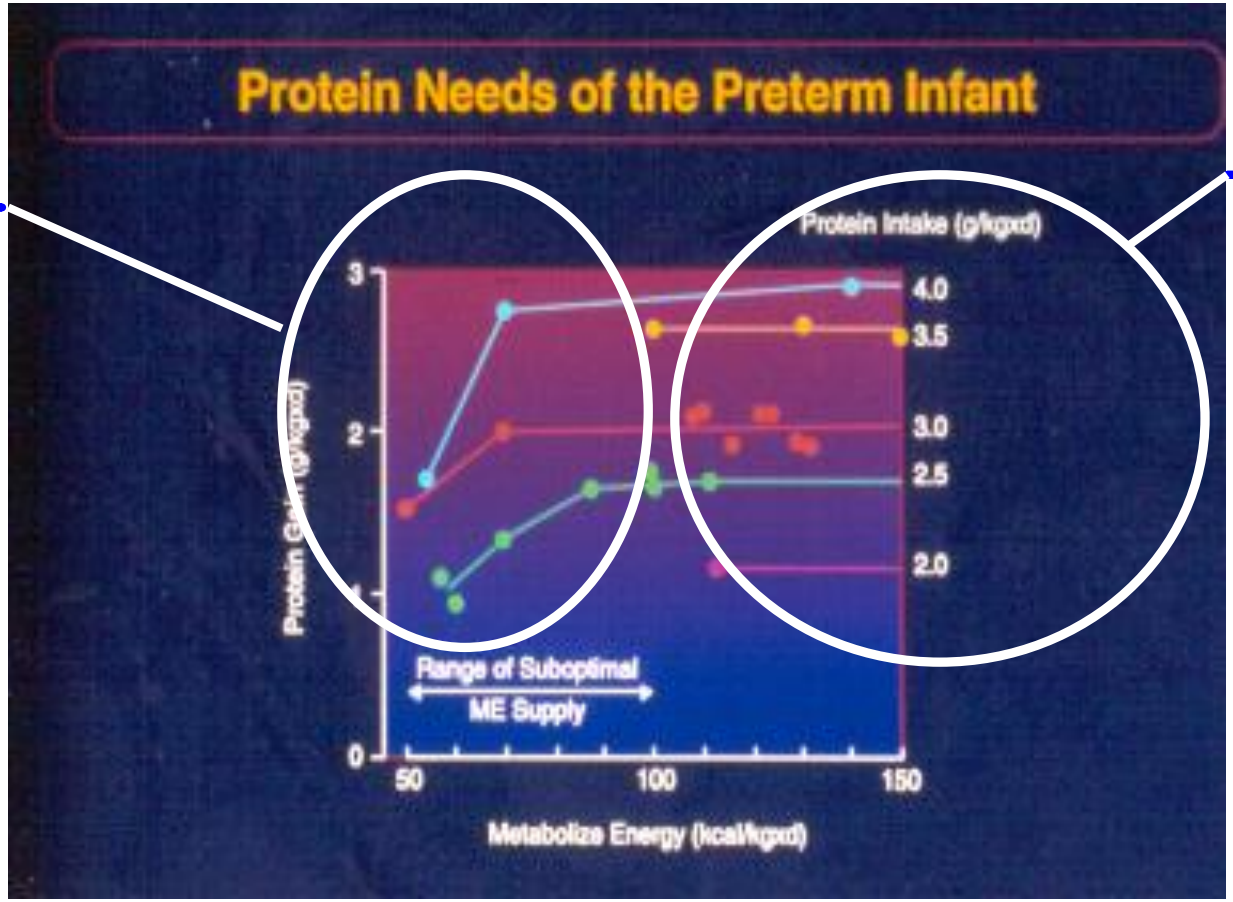
The unjustified fixation on a continuous 30 Kcal / g protein ratio.

Actually, excessive caloric intake does to a preterm infant just what it does to you and me--

makes them fatter !

Above ~80 non-protein kcal/kg/d, no further increase in protein gain for an increase in energy intake (protein gain primarily depends on protein intake!)

At lower energy intakes, protein accretion is augmented by more protein, but also more energy.



At higher energy intakes, protein accretion is augmented by more protein, but not more energy, which if added, would produce more fat.

Micheli JL, Schutz Y. Protein. In: Tsang RC et al, eds. *Nutritional Needs of the Preterm Infant*. Pawling, NY: Caduceus Medical Publishers; 1993:29-46

“Nutrients” for Preterm Infants

- **Glucose**
- **Lipids**
- **Amino Acids**
- **Insulin**

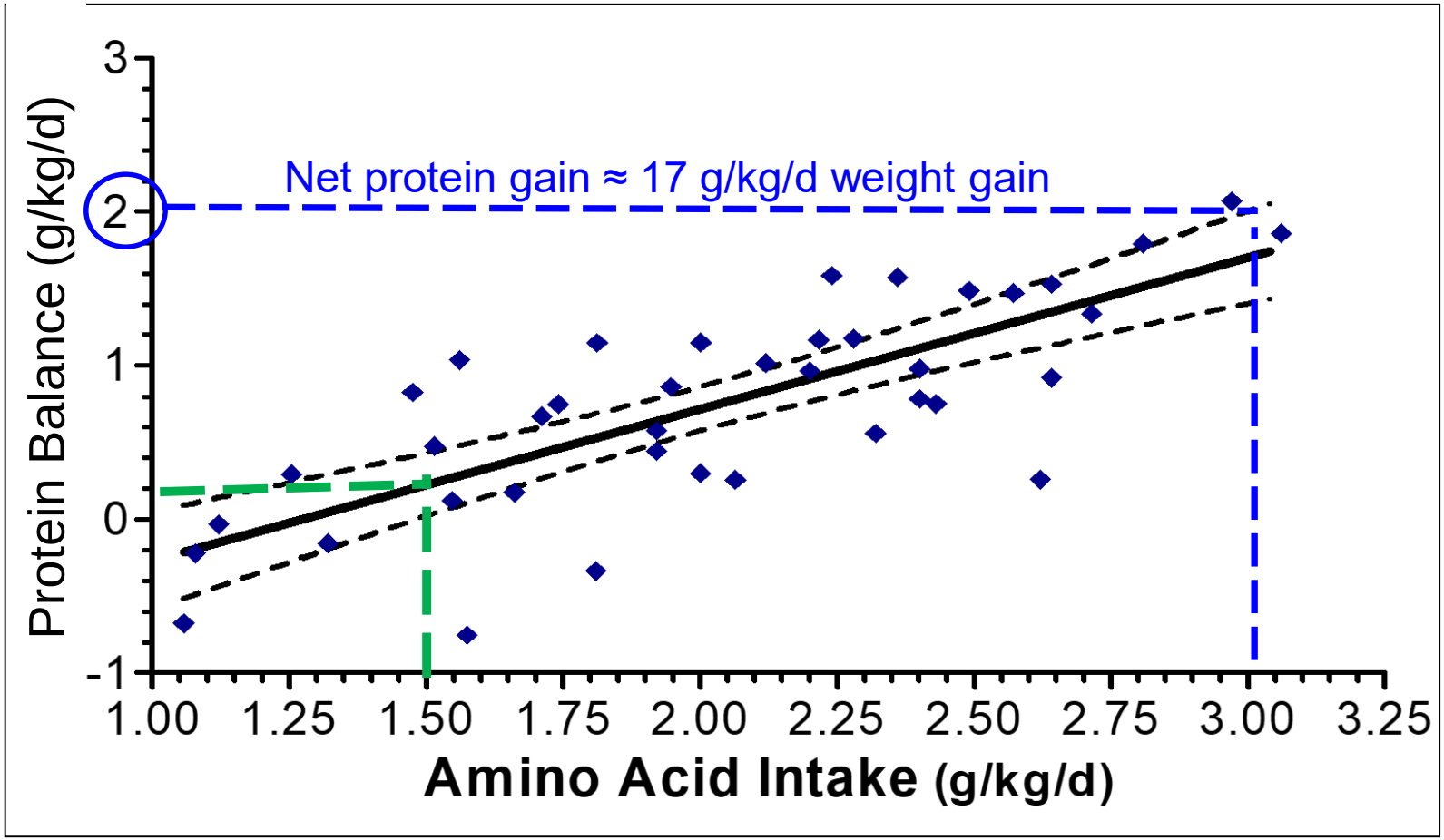
IV Amino Acids

Primary Concern—

Very preterm, VLBW and ELBW infants cannot use higher amino acid intakes to promote protein accretion.

Actually, the data show just the opposite.

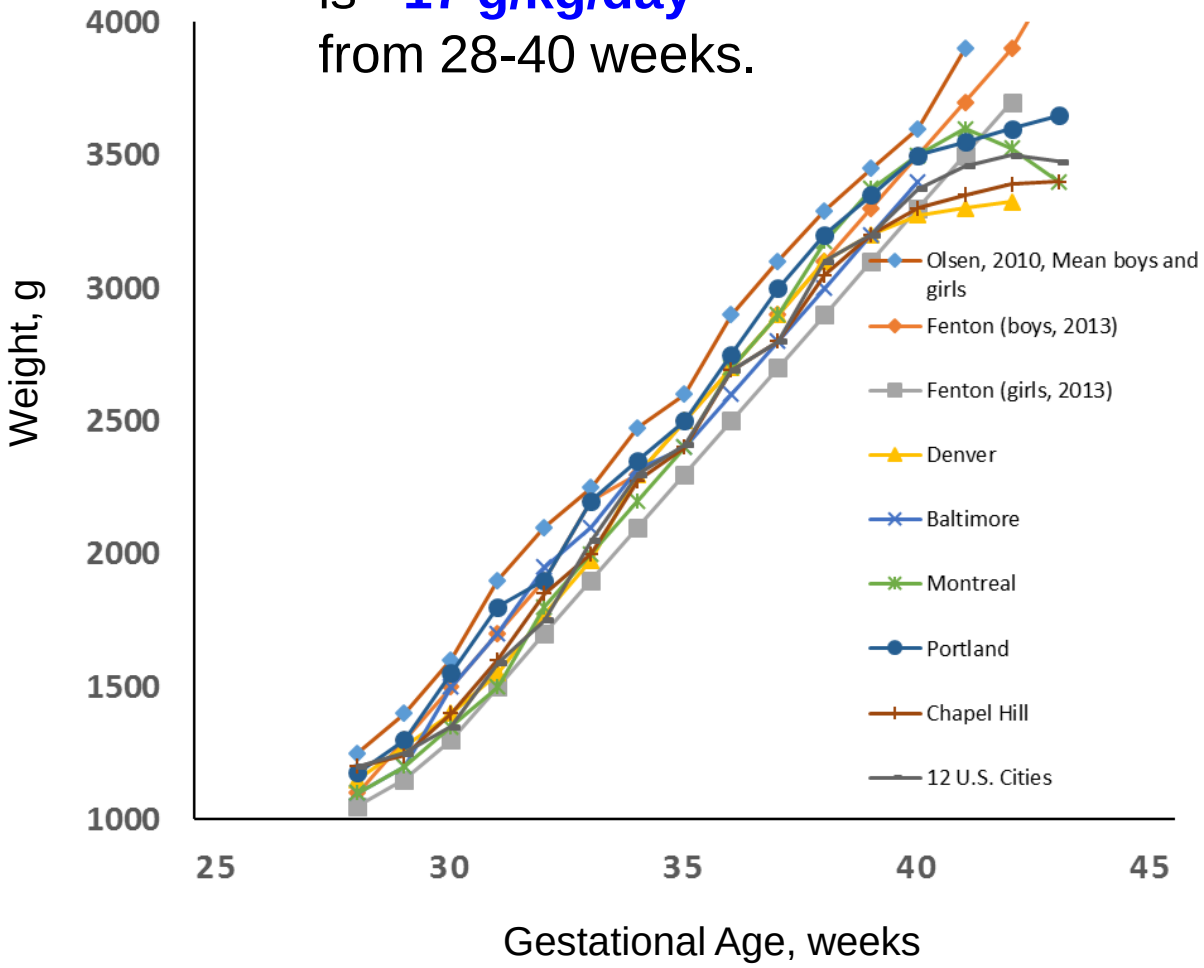
Even right after birth (24-48 hrs), and in unstable infants, there is a direct correlation between amino acid supply and protein balance, through at least 3 g/kg/day.



Thureen, et al.

Why is 17 g/kg/day important?

Because, regardless of the growth curve, the normal *average* human fetal growth rate is **~17 g/kg/day** from 28-40 weeks.



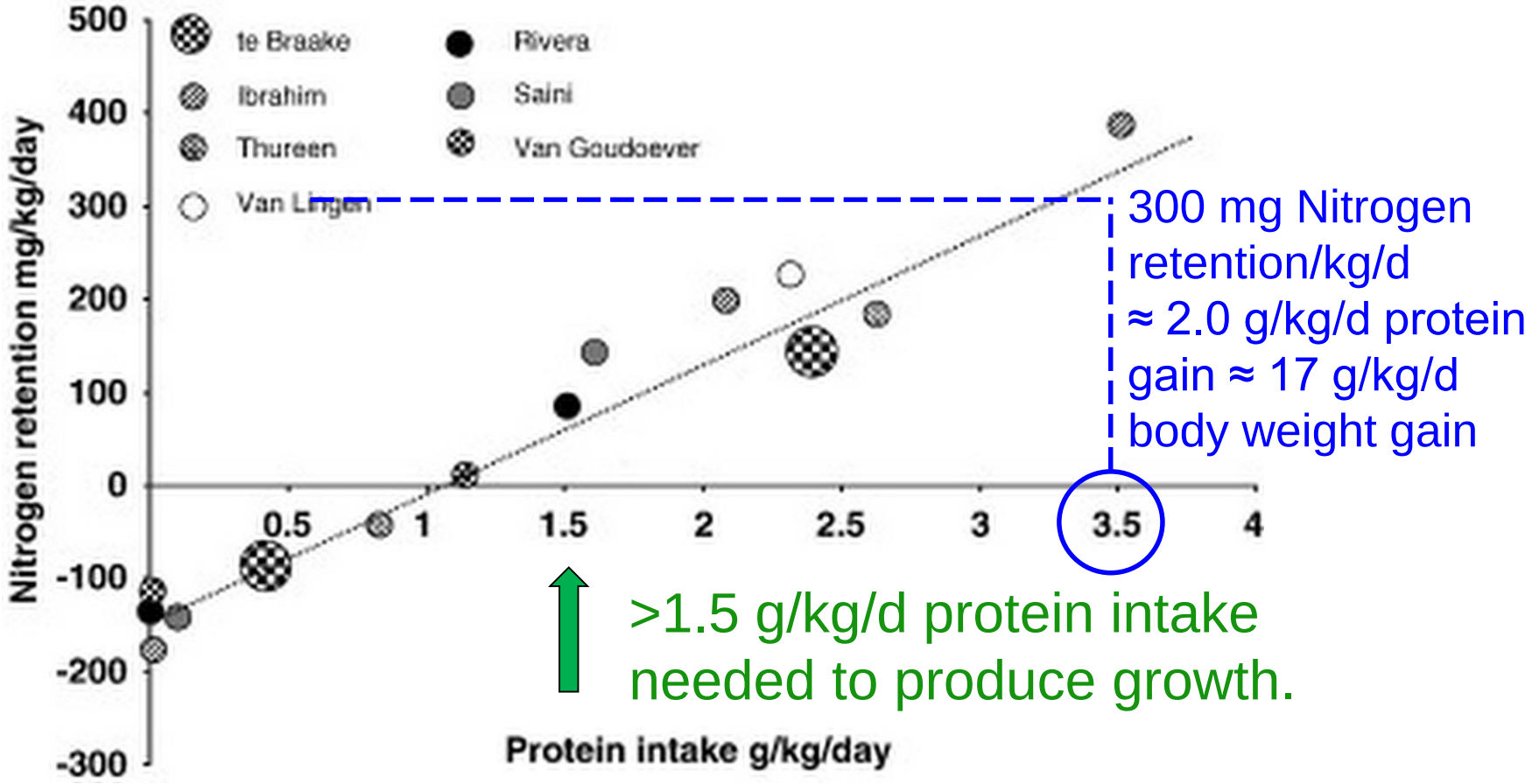
Birth weights by gestational age

From six sources adapted from Naeye R, Dixon J. Pediatr Res 1978;12:987-991;

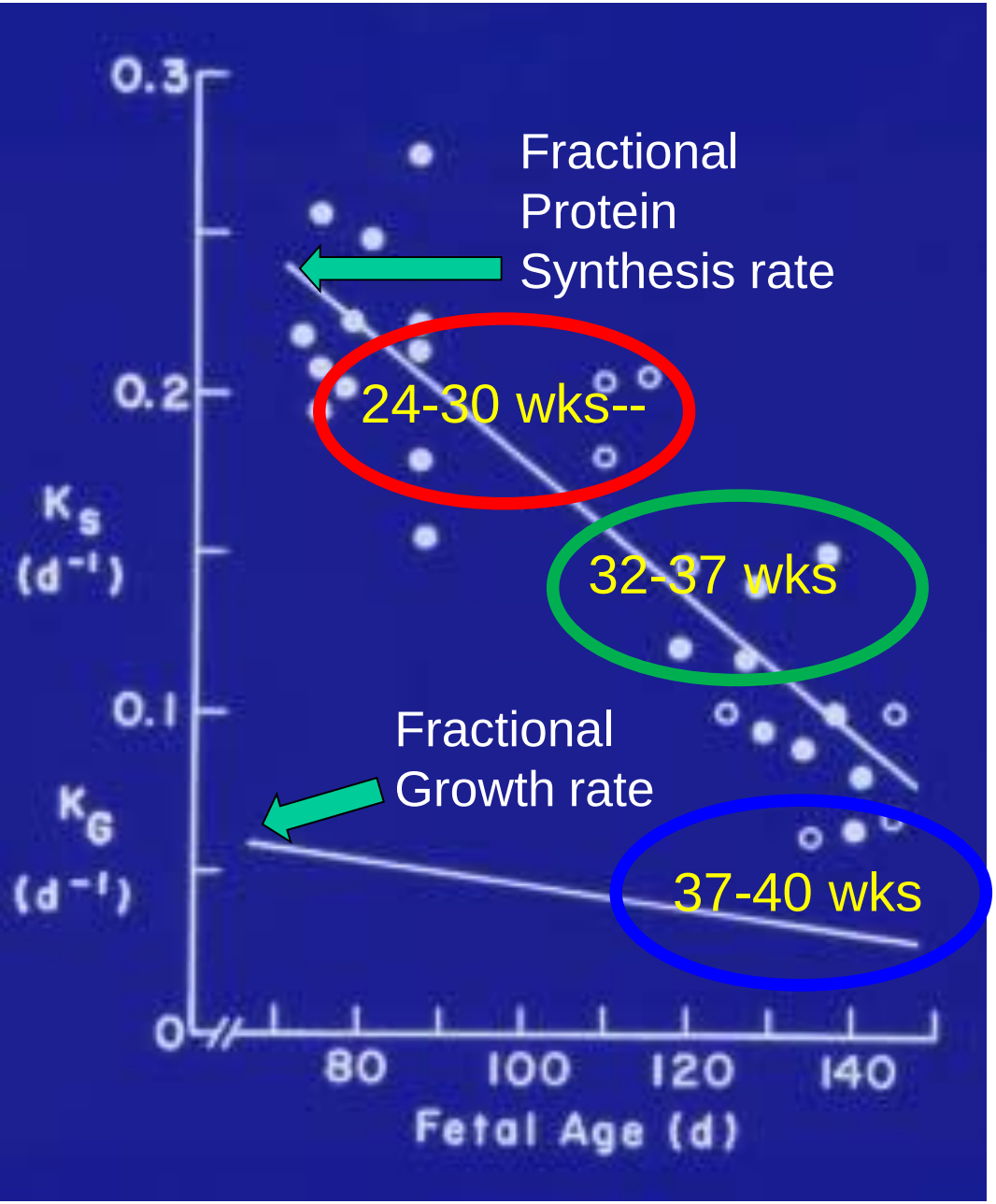
Fenton TR, Kim JH. BMC Pediatr 2003;13:59;

Olsen IE, et al. Pediatrics 2010; 125:e214-e224.

And this is true across many studies, showing that nitrogen retention (protein balance) is directly and linearly related to protein intake in preterm infants.



Embleton ND. Early Human Development 83: 831–837, 2007.



The key is the right amount at the right time!

Between 24 and 30 weeks, amino acid requirements = 3.6-4.8 g/kg/day.

Between 32 and 37 weeks, fractional growth rate decreases, as does the protein requirement for growth, to *2.5-3.5 g/kg/day*.

At term, protein requirements decrease to those of the normal breast fed infant, or 1.5-2.0 g/kg/day.

And perhaps if given long enough--duration.

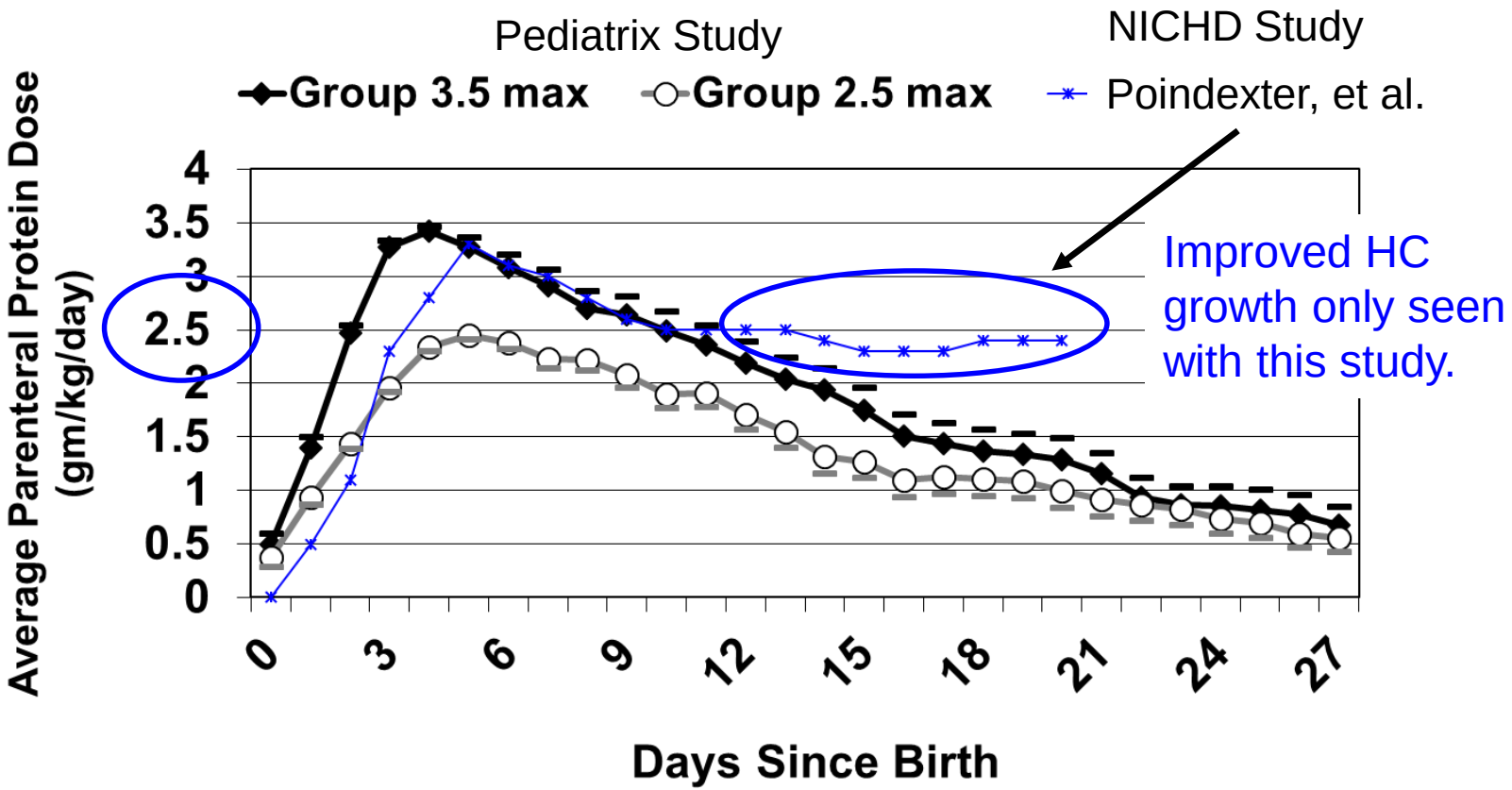
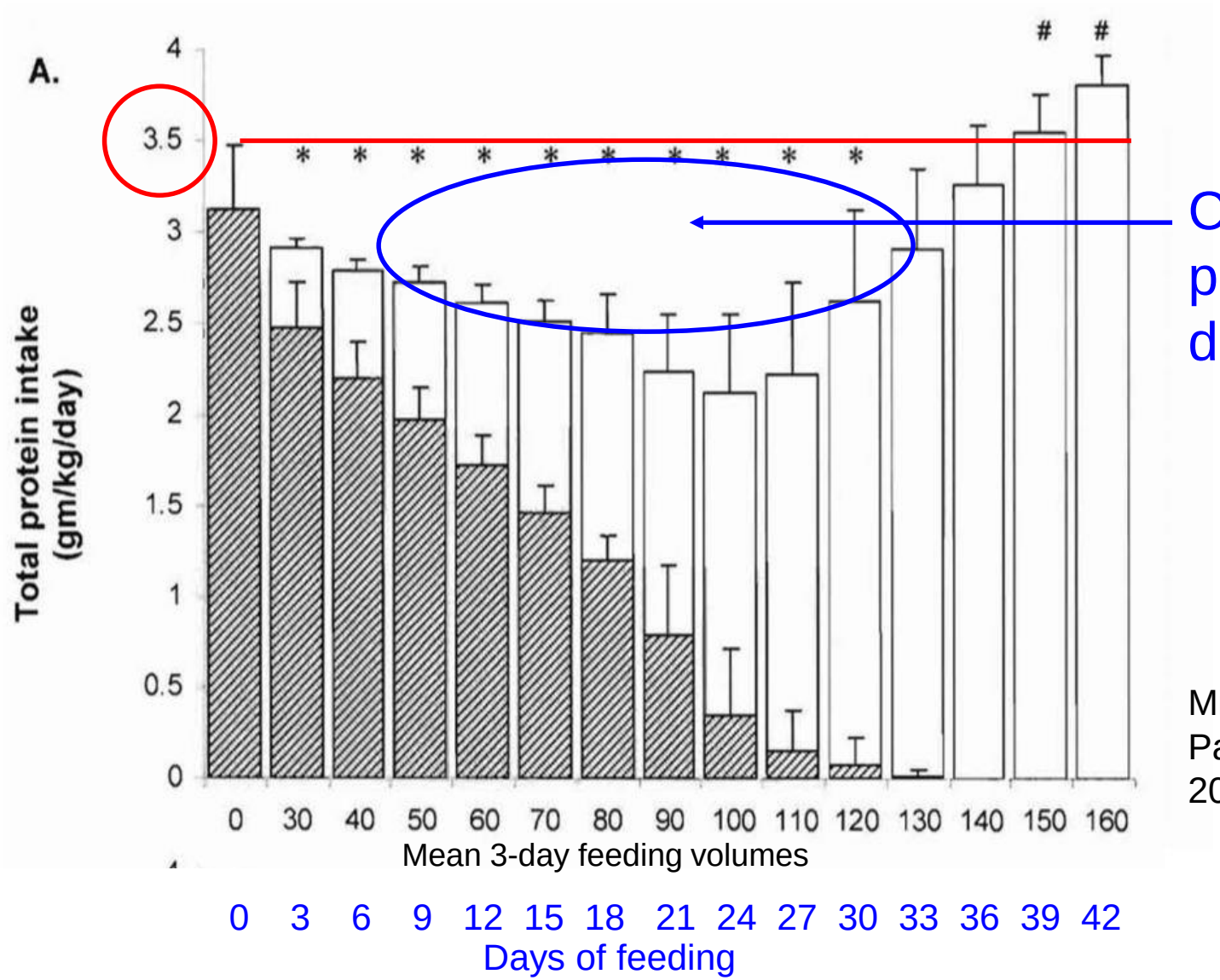


Figure courtesy of Clark RH, Chace DH, Spitzer AR; Pediatrix Amino Acid Study Group. *Pediatrics*. 2007;120:1286-1296; Poindexter B, et al. *J Pediatrics*. 2006;148:300–305.

Why long enough? Because total protein intake can fail to meet requirements when IV nutrition is weaned ahead of sufficiently increased enteral nutrition.



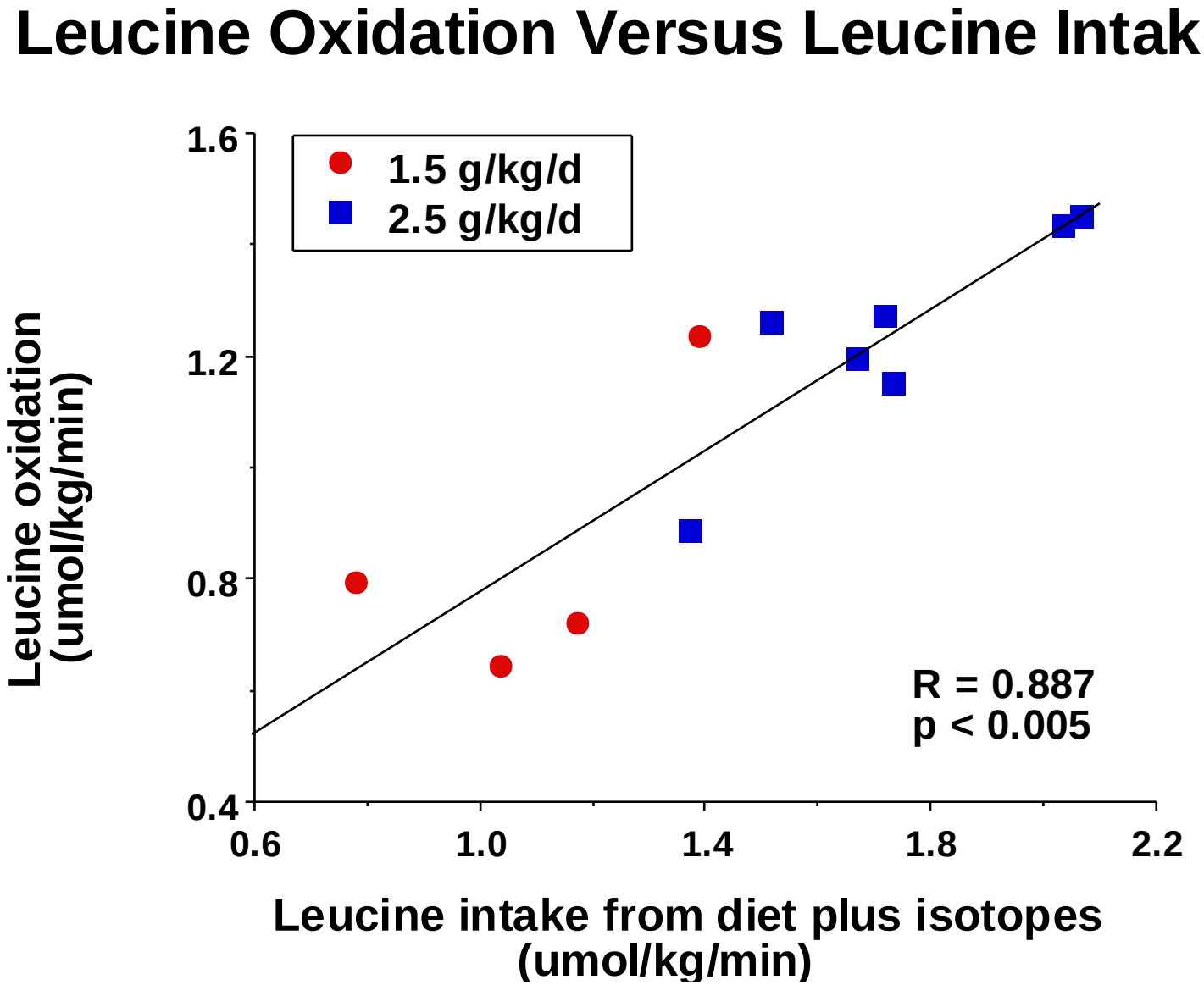
Miller M, et al. J Parent Ent Nutr 2014;38:489-497.

Concerns---

- **The excess amino acids with higher intravenous and/or enteral protein intake won't be oxidized.**

Actually, they are.

At lower energy intakes, Amino Acids can provide calories.



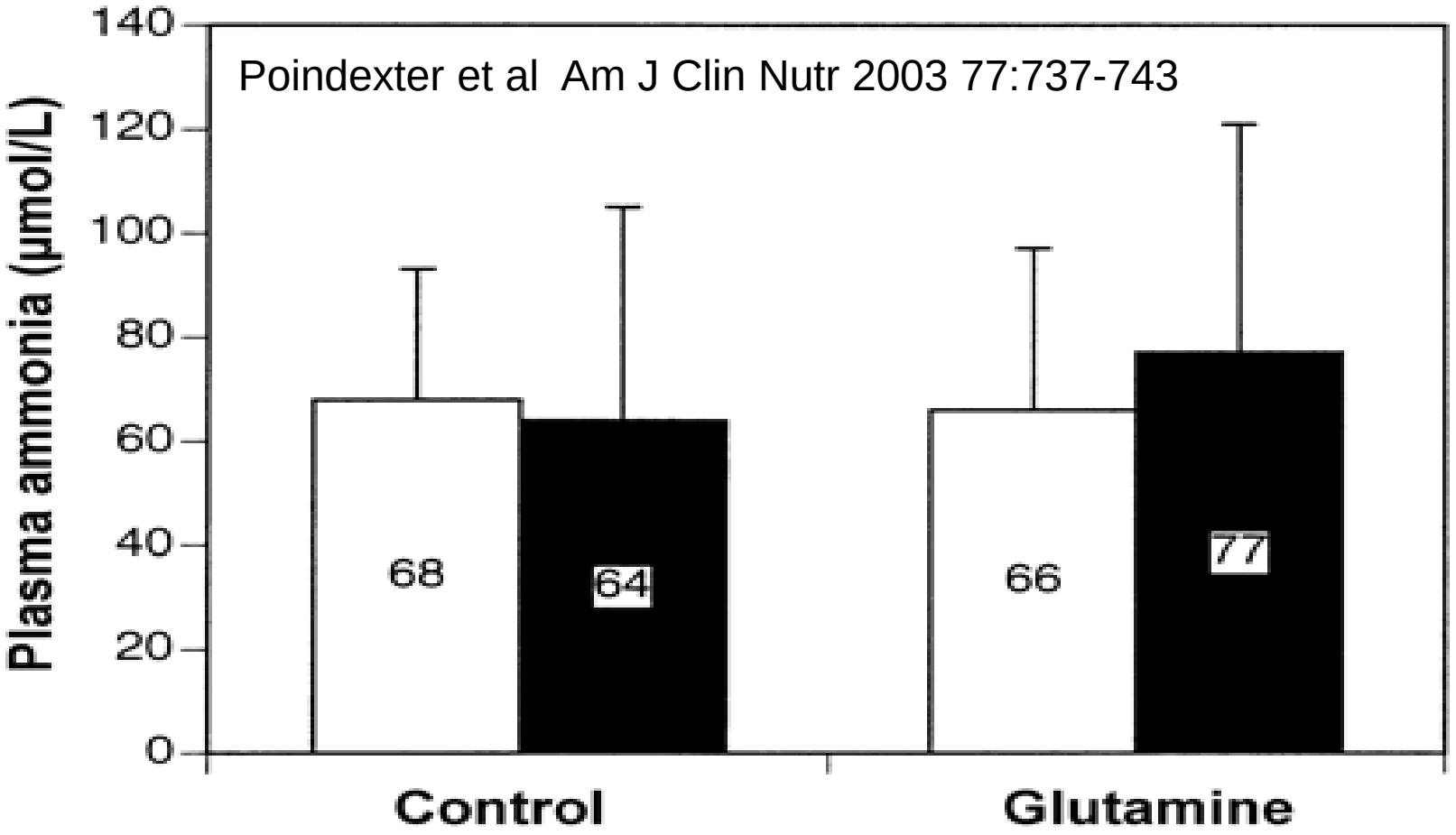
Concerns---

- **Excessive amino acid and/or protein intake can lead to *Hyperammonemia*.**

  Actually, this does not appear to occur as often or as severely as suggested due to very rapid amino acid oxidation, urea synthesis, and synthesis into amino acids.

Plasma Ammonia on TPN

Neonatal Network Trial : Effects of Glutamine Supplementation
TPN with or without Gln at 3 gm/kg/day



If a baby is hyperammonemic, it is much more likely because of liver failure.

Concerns---

Excessive amino acid and/or protein intake can lead to *uremia* due to decreased GFR.

Actually, this does not appear to occur as often or as severely as suggested due to low urinary concentrating capacity and relatively high urinary flow rates.

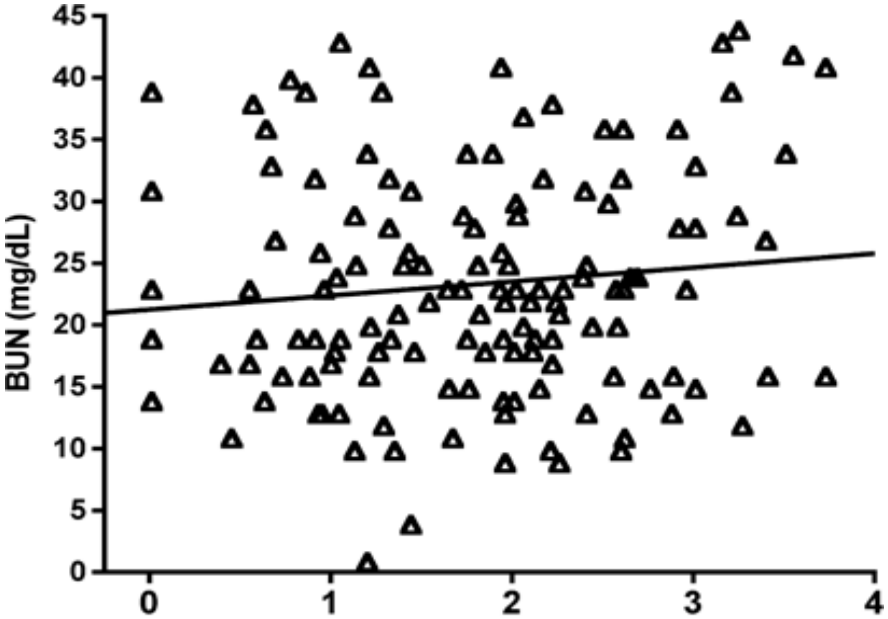
And an increase in urea production should occur to the extent that amino acids are oxidized, which clearly is the case.

Most studies show that---

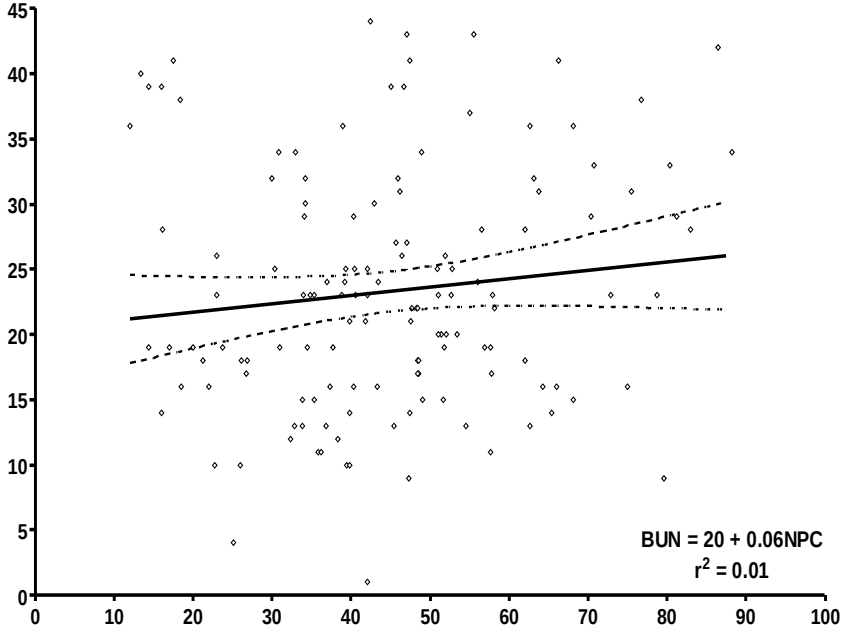
BUN correlates poorly with amino acid intake

Or with non-protein caloric intake

(data in <1000 g BW infants)



Amino Acid intake, g/kg/d



Non-protein caloric intake, kcal/kg/d

Ridout, et al. *J Perinatology* 2005; 25:130−133

Concerns---

- **Excessive amino acid and/or protein intake can lead to *metabolic acidosis*.**

  Actually, this doesn't occur very often,

  unless there are other reasons for reduced GFR and urine flow rate,

  -- such as severe fluid restriction as often done for hyperglycemia, severe PDAs, or indomethacin Rx,

  -- or over interpreted, due to dilutional acidosis from excessive fluid administration.

Concerns—

Very preterm, VLBW infants are incapable of tolerating higher amino acid and protein intakes and do not grow better.

For example--

	HAA: 4.0 g/kg/d	SAA: 2.5 g/kg/d	p
Wt gain, g/kg/d Birth to 1800g	16.1 ± 2.0	16.6 ± 2.4	0.94
Wt gain, g/kg/d Regained BW to 36 wk PMA	16.0 ± 2.7	16.6 ± 2.4	0.32

At 2 years:	HAA	SAA	p
Weight Z score:	−0.17 ± 1.12	−0.22 ± 1.31	0.84
Length Z score:	0.57 ± 1.12	0.61 ± 1.25	0.86
OFC Z score:	−0.56 ± 1.3	−0.57 ± 1.2	0.97

Burattini I, et al. J Pediatr 2013; 163:1278–1282.

But note—weight and OFC still negative.

One Extra Gram of Protein to Preterm Infants, Birth to 1800 g: A Single-Blinded Randomized Clinical Trial

At 2 years:	Hi Prot	Stand Prot	p
Weight SDS:	−0.1 ± 1.31	−0.09 ± 0.96	0.96
Length SDS:	0.79 ± 1.34	0.66 ± 1.02	0.53
OFC SDS:	−0.94 ± 1.39	−1.01 ± 1.42	0.77

Bellagamba M, et al. J Pediatr Gastroenterol Nutr 2016; 62:879–884.

Nutritional deficiency?

or other cause?

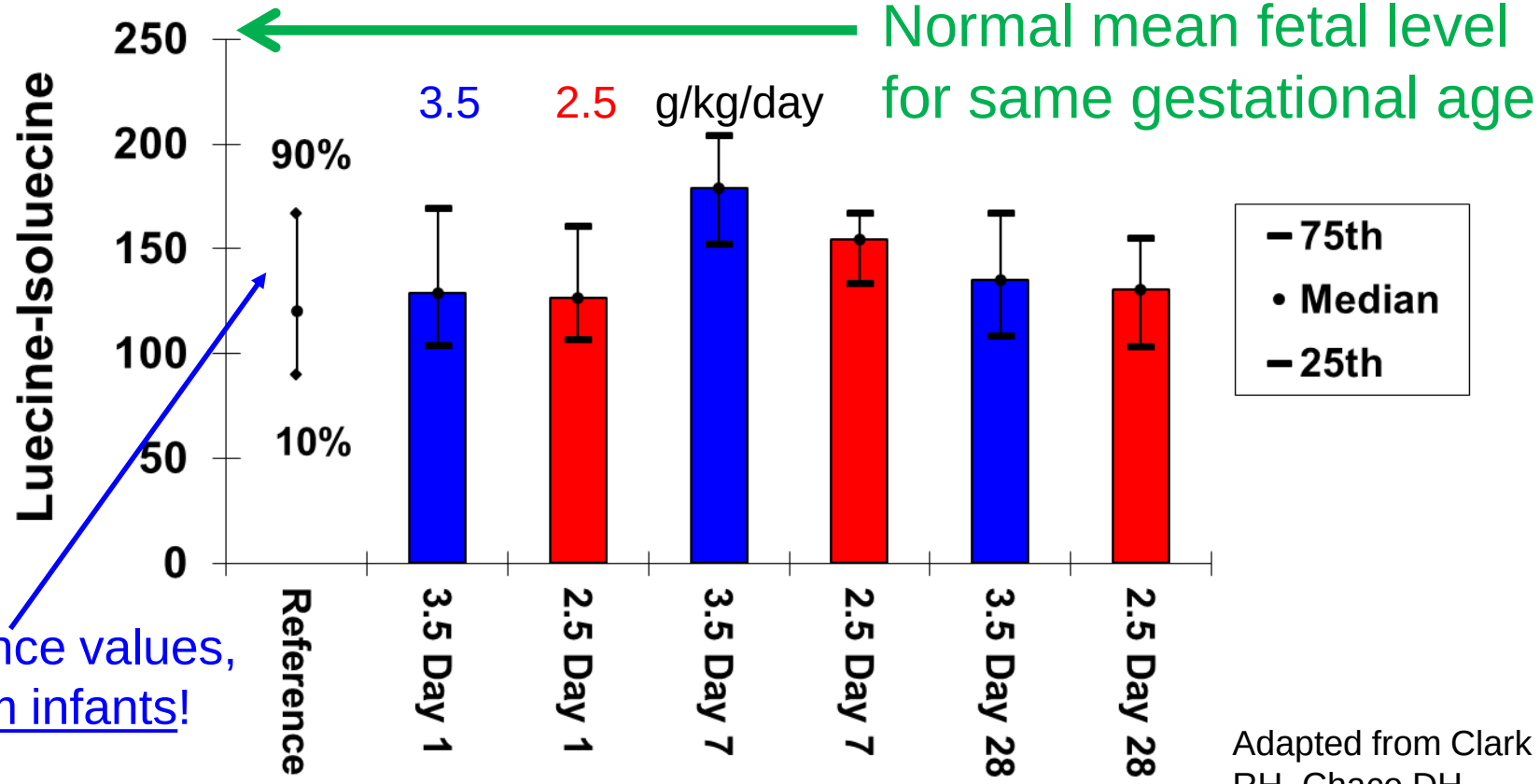
Concerns—

Actually, insufficient amino acids, primarily essential but also conditionally essential, is a more common problem,

and likely why postnatal growth in very preterm infants, particularly of the brain, is restricted.

Even at 3.5 g/kg/day (if actually achieved), there may be inadequate essential amino acids.

Sum of Leucine and Isoleucine concentrations



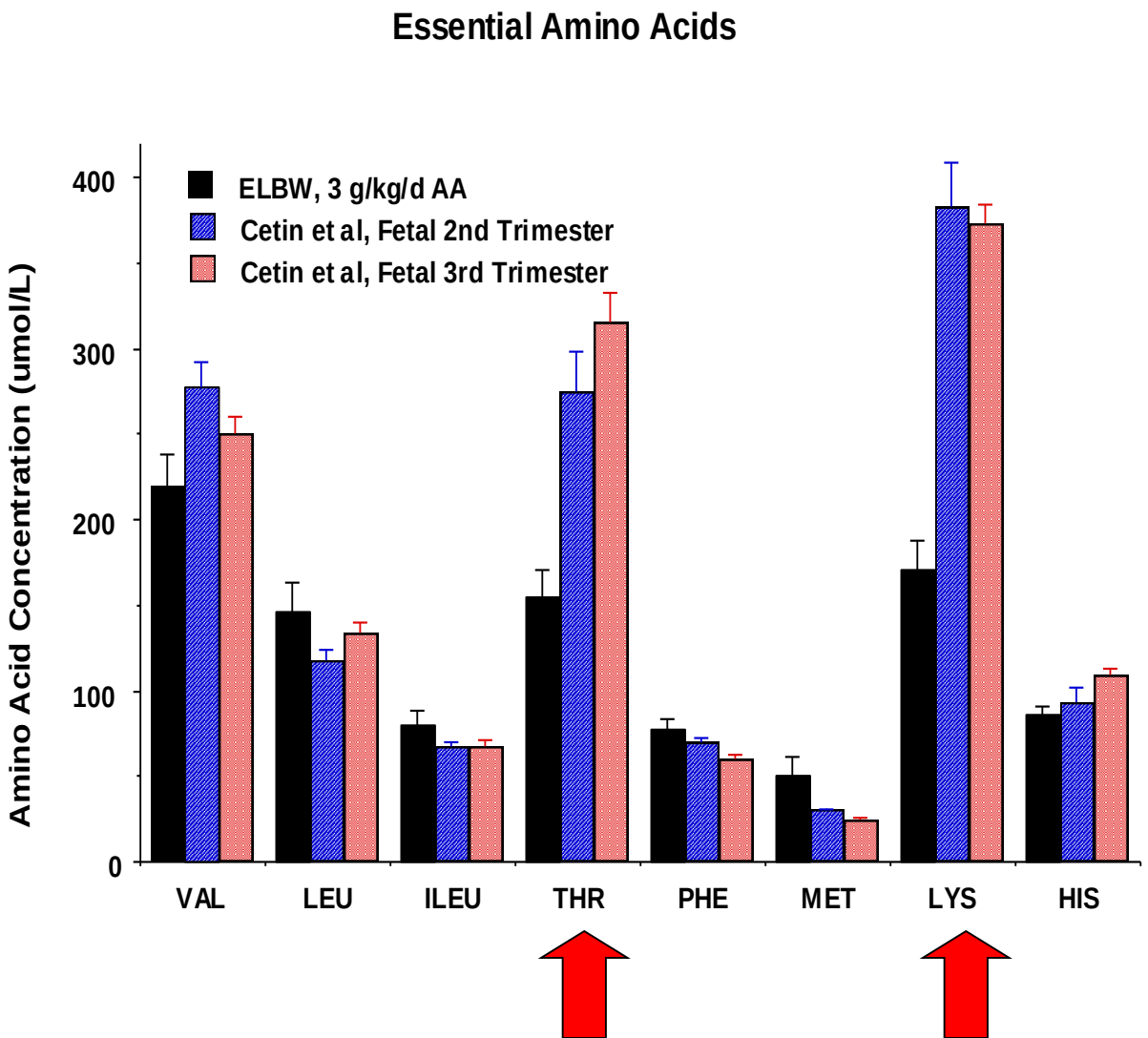
Reference values, for Term infants!

Thus, these infants had only half to 2/3 of normal plasma concentrations of *at least* 2 essential amino acids.

A likely cause of their growth limitation?

Adapted from Clark RH, Chace DH, Spitzer AR; Pediatrix Amino Acid Study Group. Pediatrics 2007;120:1286-1296.

Individual Amino Acids – even at 3 g/kg/d there still is room for improvement!

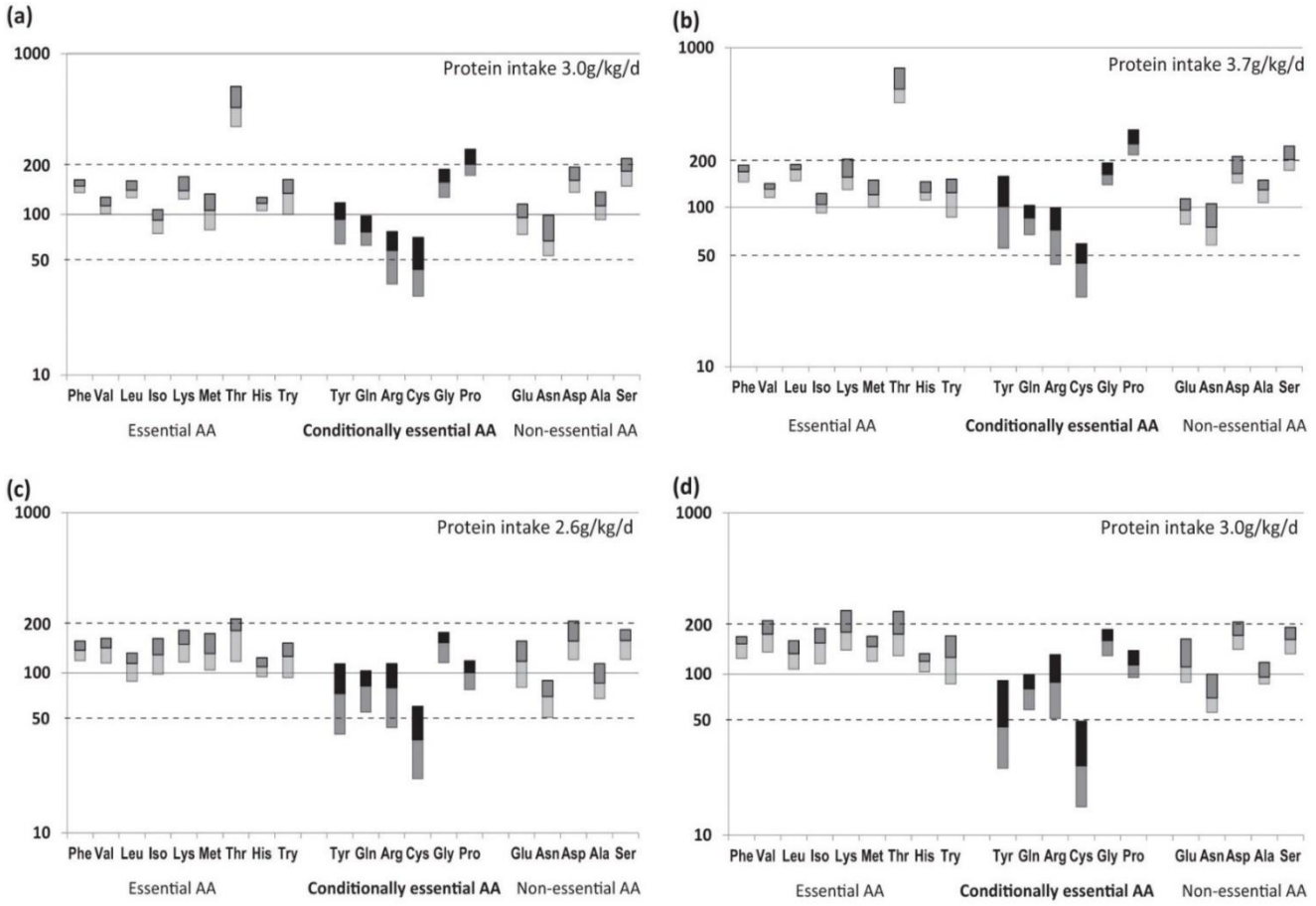


Even at high amino acid infusion rates, current IV Amino Acid solutions may not produce normal (fetal) concentrations of all essential amino acids, which "will" limit growth.

(Thureen and Hay)

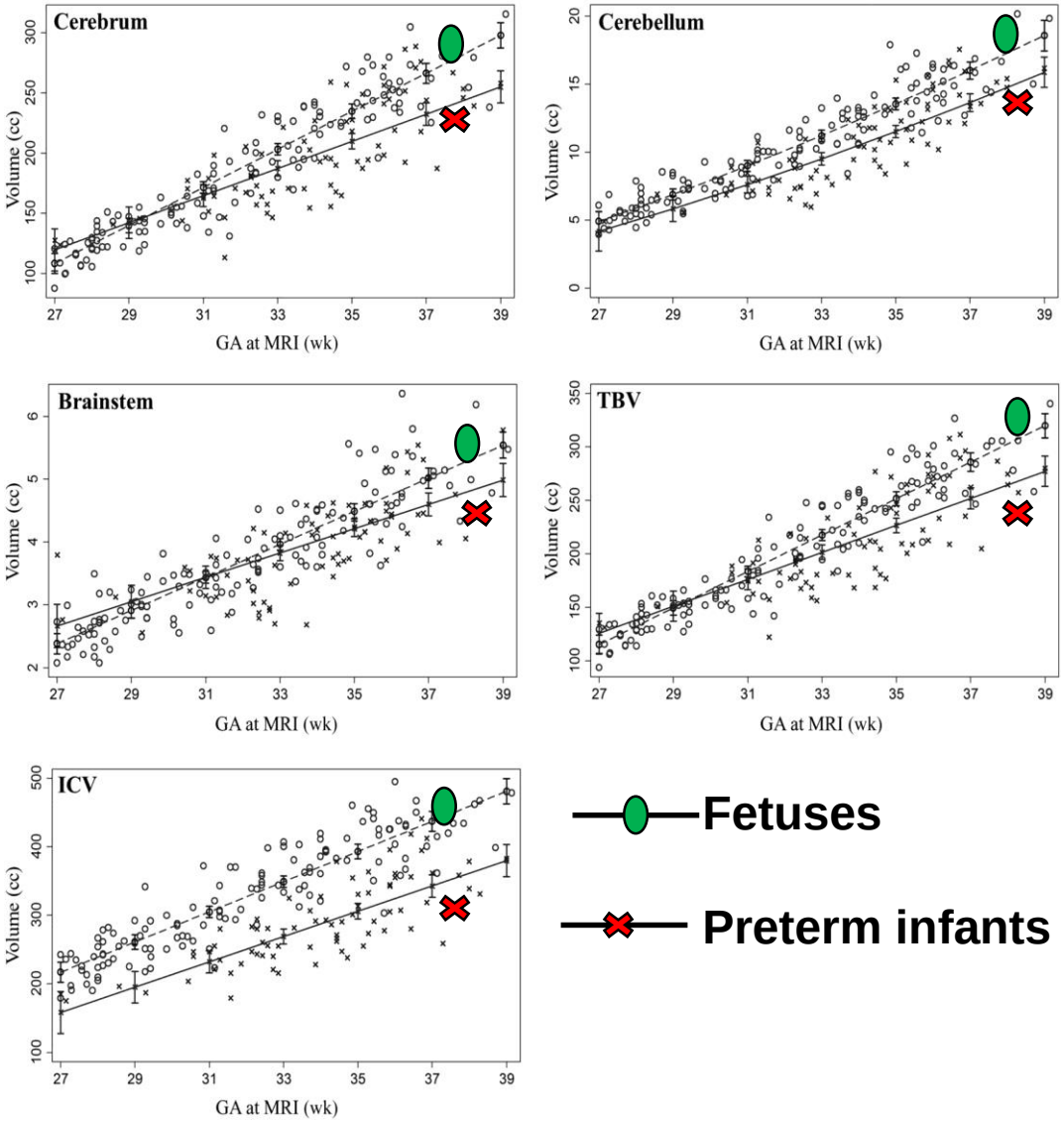
High AA infusion rates also do not prevent low plasma levels of conditionally essential amino acids (tyrosine, glutamine, arginine, cysteine, glycine, proline) in very preterm infants.

Morgan C, Burgess L.. JPEN 2015 Jul 6. pii: 0148607115594009. [Epub ahead of print]



The point is, more of an unbalanced Amino Acid solution does not guarantee optimal plasma AA concentrations or related metabolic and growth responses.

Brain volumes by MRI plotted against GA in preterm and fetal cohorts (controlling for sex).



Preterm infant brain growth <u>slower in all regions</u> than in the normally growing fetus.

Marine Bouyssi-Kobar et al. Pediatrics 2016;138:e20161640

PEDIATRICS®

In response to reports suggesting that early, high infusion rates of AA solutions might not improve various outcomes—

1. Early—day 1-3—period has many physiological and biochemical problems for which current IV amino acid solutions were not designed.

2. Positive protein balance can occur during this period, even without measurable increases in weight, length, or OFC.

3. Plasma AA levels in PN-fed preterm infants show an imbalance in essential and conditionally essential AAs with current neonatal AA formulations that is not improved by increasing protein intake.

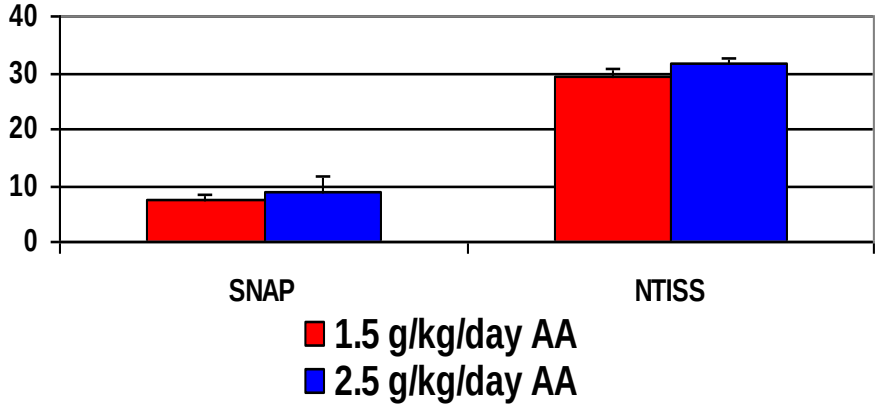
3. More protein than required for protein balance and growth do not make infants grow faster or bigger.

But—Less than needed essential IV AAs results in reduced protein balance and slower growth, and contributes to smaller head circumferences and worse neurodevelopmental outcomes.

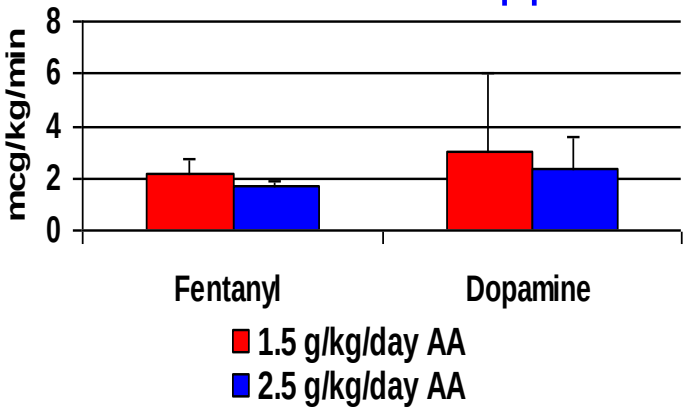
We need more studies in preterm infants who are sick and physiologically unstable, such as this one in near term infants undergoing complex, stressful abdominal surgery, comparing moderate vs. higher IV amino acid infusions.

Reynolds RM, Bass KD, Thureen PJ. J Pediatr 2008;152:63-67

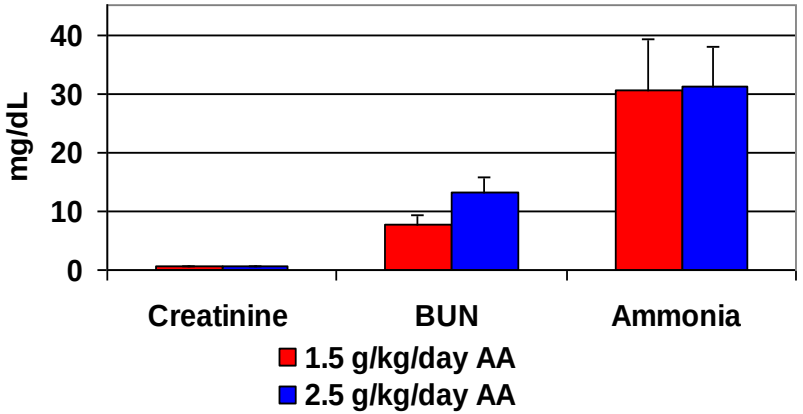
Moderate Severity of Illness



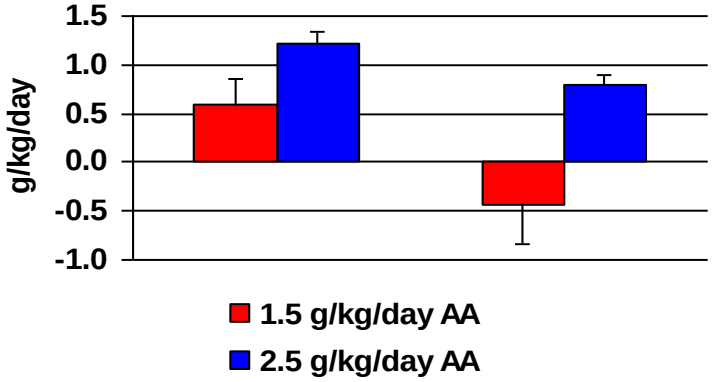
Moderate analgesic and catecholamine support



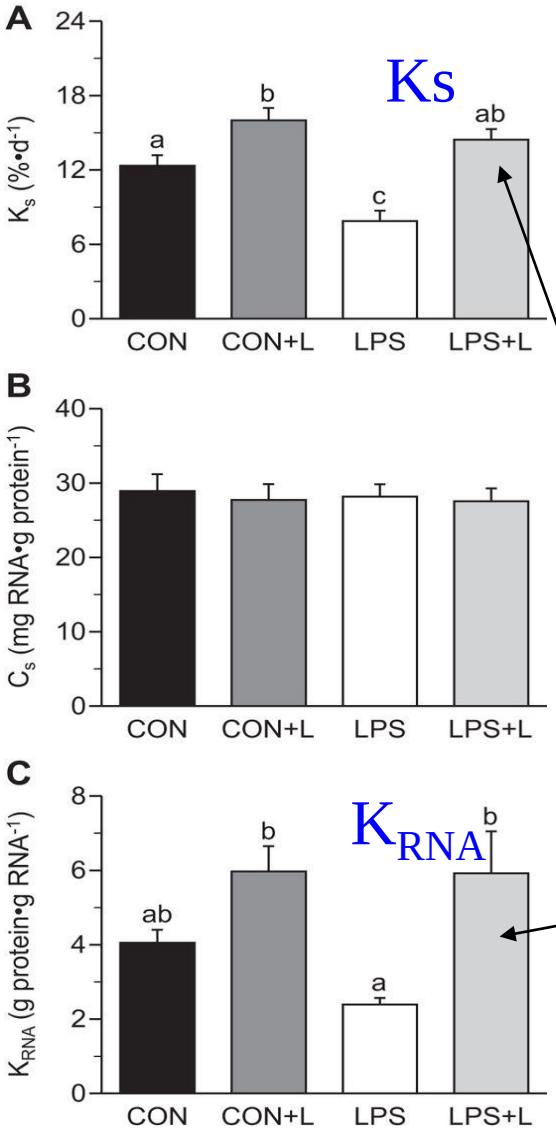
No evidence of protein toxicity



Positive Protein Balance



IV Amino Acids during sepsis? Probably yes!



A. Fractional rates of protein synthesis (KS)

B. Protein synthetic capacity (CS)

C. Protein synthetic efficiency (K_{RNA})

in longissimus dorsi muscle of piglets infused with Leucine during endotoxemic pancreatic-substrate clamps.

Leucine specifically improves

Ks

K_{RNA}

despite endotoxemia.

Hernandez-García AD, et al.
Am J Physiol Endocrinol Metab 2016;311:E791-E801

“Nutrients” for Preterm Infants

- **Oxygen**
- **Glucose**
- **Lipids**
- **Amino Acids**
- **Insulin**

Insulin

In preterm infants, there still is no evidence that insulin infusion to "enhance" nutrition is beneficial, and there are many potential problems (lots of episodes of hypoglycemia!; increased cortisol and higher blood pressure).

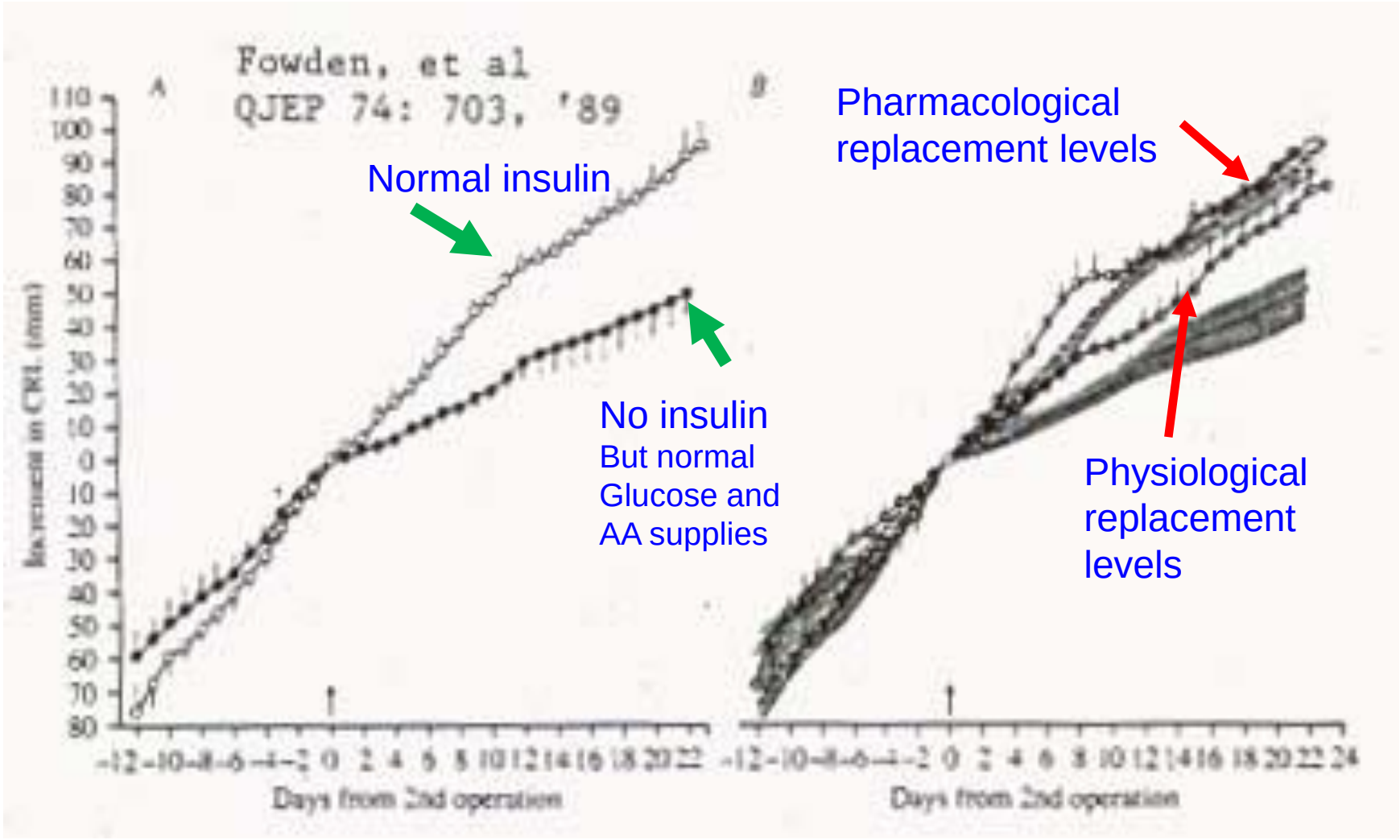
NIRTURE Trial: Beardsall K, et al. *BMC Pediatr*. 2007;7:29-38.

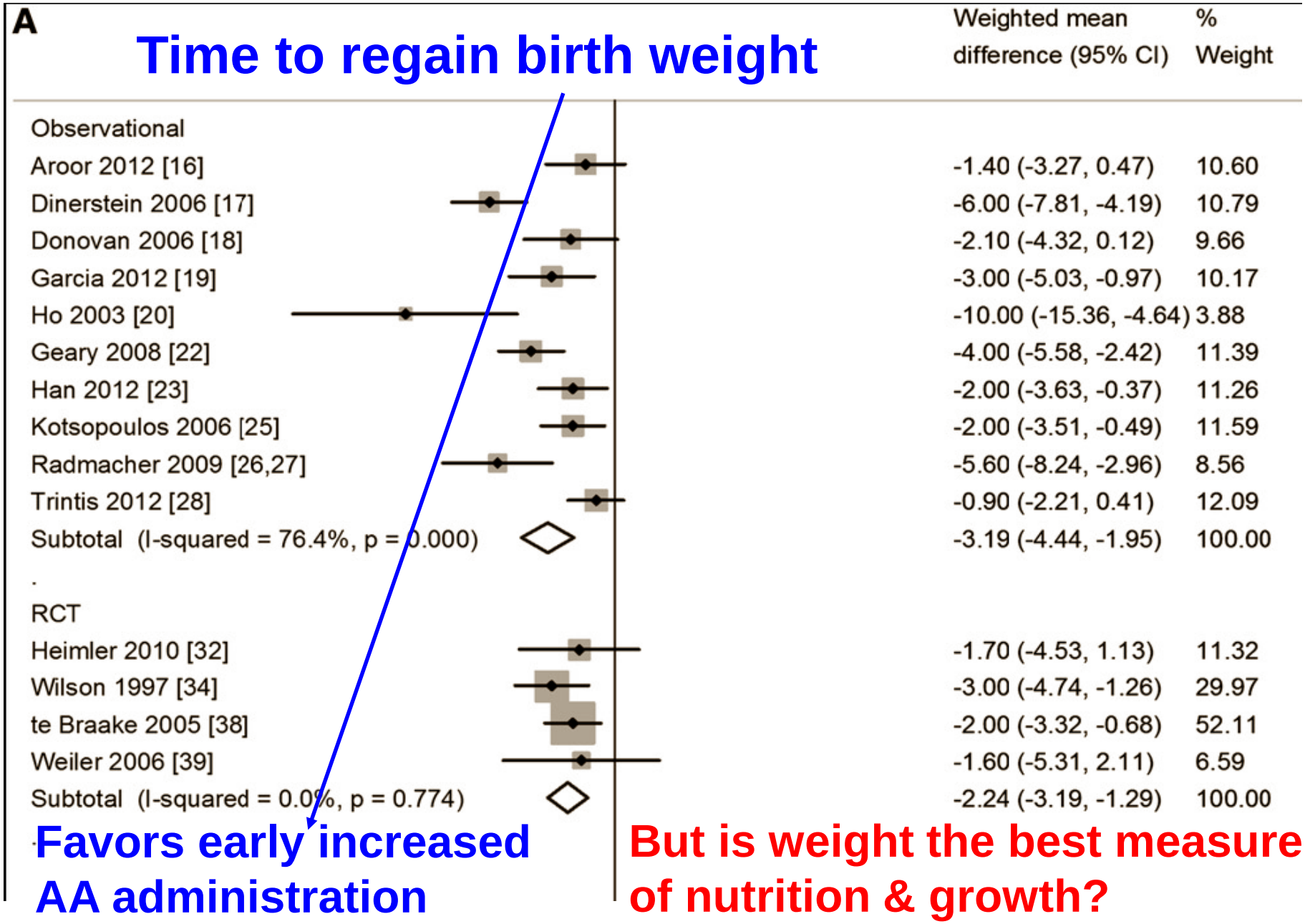
For the most part, insulin treatment to increase growth will simply make the baby fatter (and produce pathologically fatty livers and hearts and promote systemic inflammation).

No evidence that insulin increases brain glucose uptake or brain growth.

Negative feedback mechanisms limit a sustained effect of continued high insulin concentrations on amino acid synthesis into proteins and protein accretion.

Insulin replacement after pancreatectomy in fetal sheep—no extra effect on linear growth.





Moyses HE, et al. Am J Clin Nutr 2013;97:816–26.

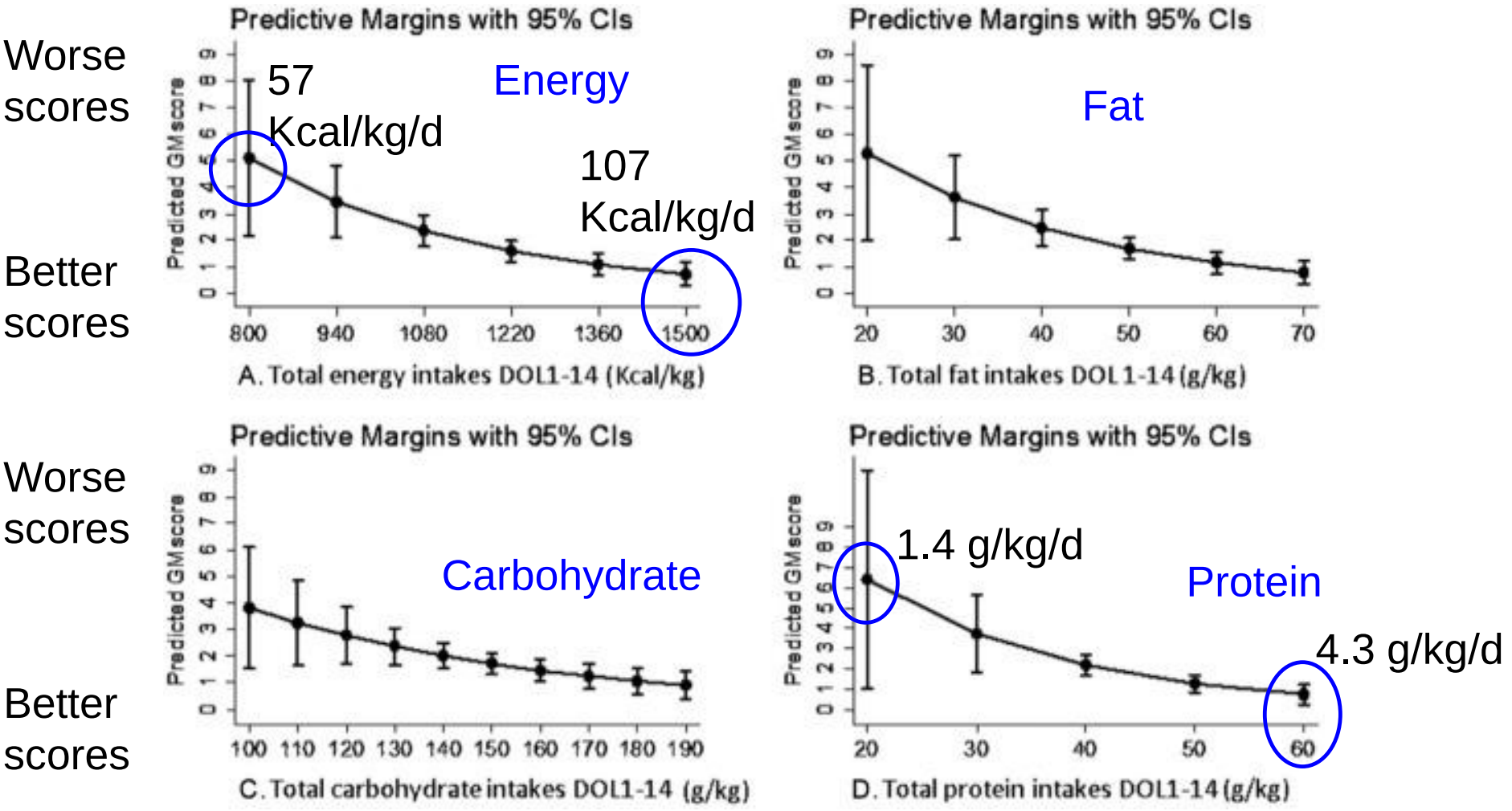
Maybe neurodevelopmental outcomes are better measures of sufficient protein and energy intakes.

First-Week Protein and Energy Intakes are associated with 18-Month Developmental Outcomes in Extremely Low Birth Weight Infants

- **Protein intake and energy intake during week 1** each had independent effects on MDI at 18 months
- **Every 1 g/kg/d increase in protein intake associated with 8.2 point increase in MDI at 18 months (both females and males)**
- **Every 10 kcal/kg/d increase in energy intake associated with 4.6 point increase in MDI at 18 months.**

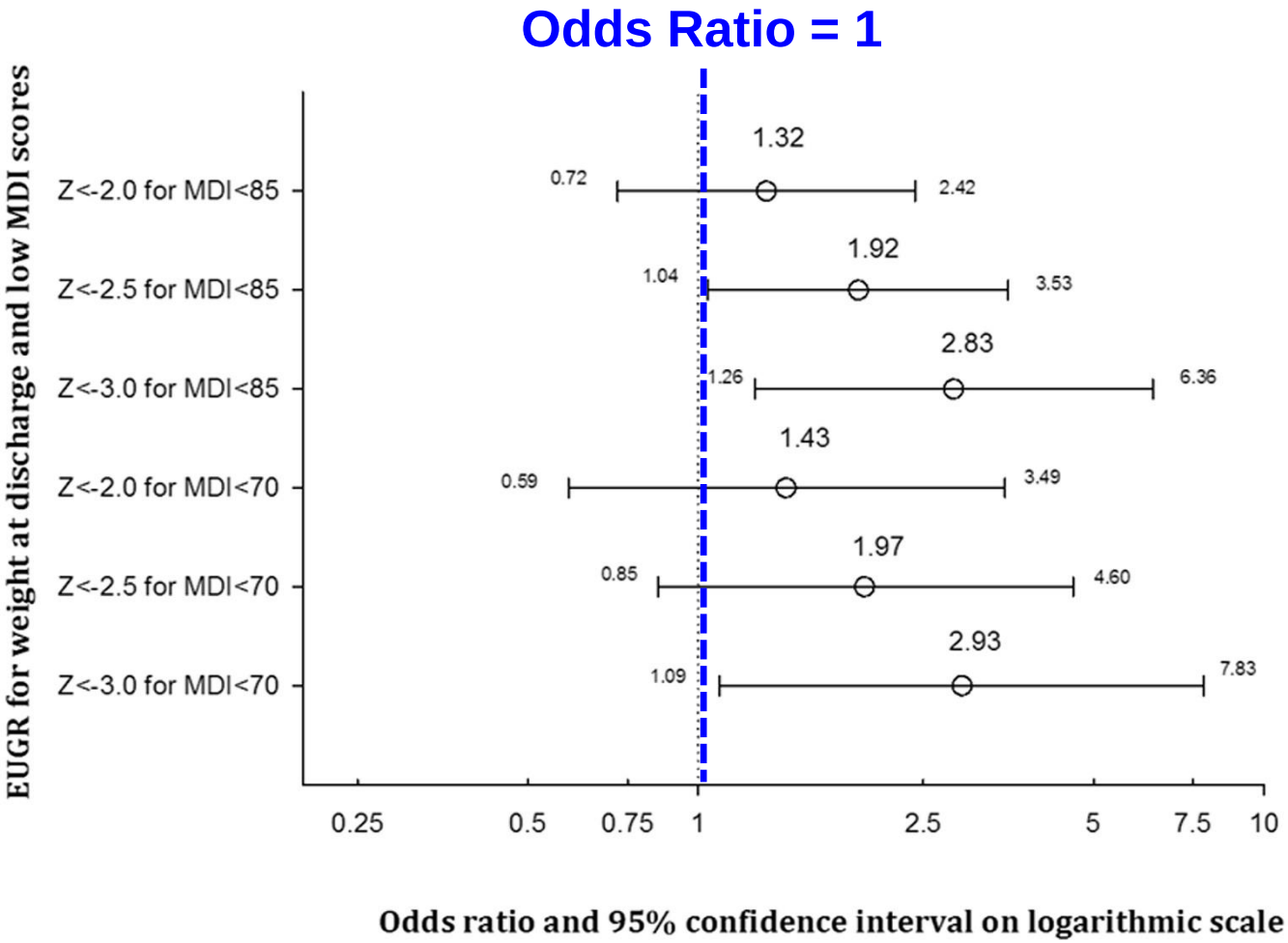
Stephens BE, et al. Pediatrics 2009;123:1337–1343

Predicted adverse MRI gray matter scores according to the cumulative total intake of A energy, B fat, C carbohydrates, and D proteins during the first 2 weeks of life (DOL1-14), after adjustments on sepsis.



Beauport L, et al. Impact of Early Nutritional Intake on Preterm Brain: A Magnetic Resonance Imaging Study. J Pediatrics 2017;181:29–36.e1.

Neurodevelopmental outcomes of infants with very low birth weights are associated with the severity of their extra-uterine growth retardation



Chien HC, et al. Pediatrics & Neonatology, DOI: 10.1016/j.pedneo.2017.08.003
Neonatology DOI: (10.1016/j.pedneo.2017.08.003)

And lean body mass, too!

First 3 Weeks Protein and Energy Intakes are positively associated with body composition benefits in 20-yr old adults born as very LBW infants.

- **Every 1 g/kg/d increase in protein intake (starting at low intakes) associated with:**
  - **22.5% higher lean body mass**
  - **22.1% higher resting energy expenditure**
- Similar associations seen with energy and fat, but not carbohydrate.
- **Energy and fat intakes were most positively associated with BMI and % body fat.**

Matinolli H-M, et al. J Nutr 2015;145:2084-2091

Fetal vs Very Preterm Neonatal Nutrition

Normal Fetal Nutrition

1. Amino acids are pumped into the fetus at rates and concentrations that are higher than the fetus can use.
2. The excess amino acid load is oxidized for energy.
3. Glucose is taken up and used to meet energy needs.

Contrasting "Customary" ELBW/VLBW Nutrition

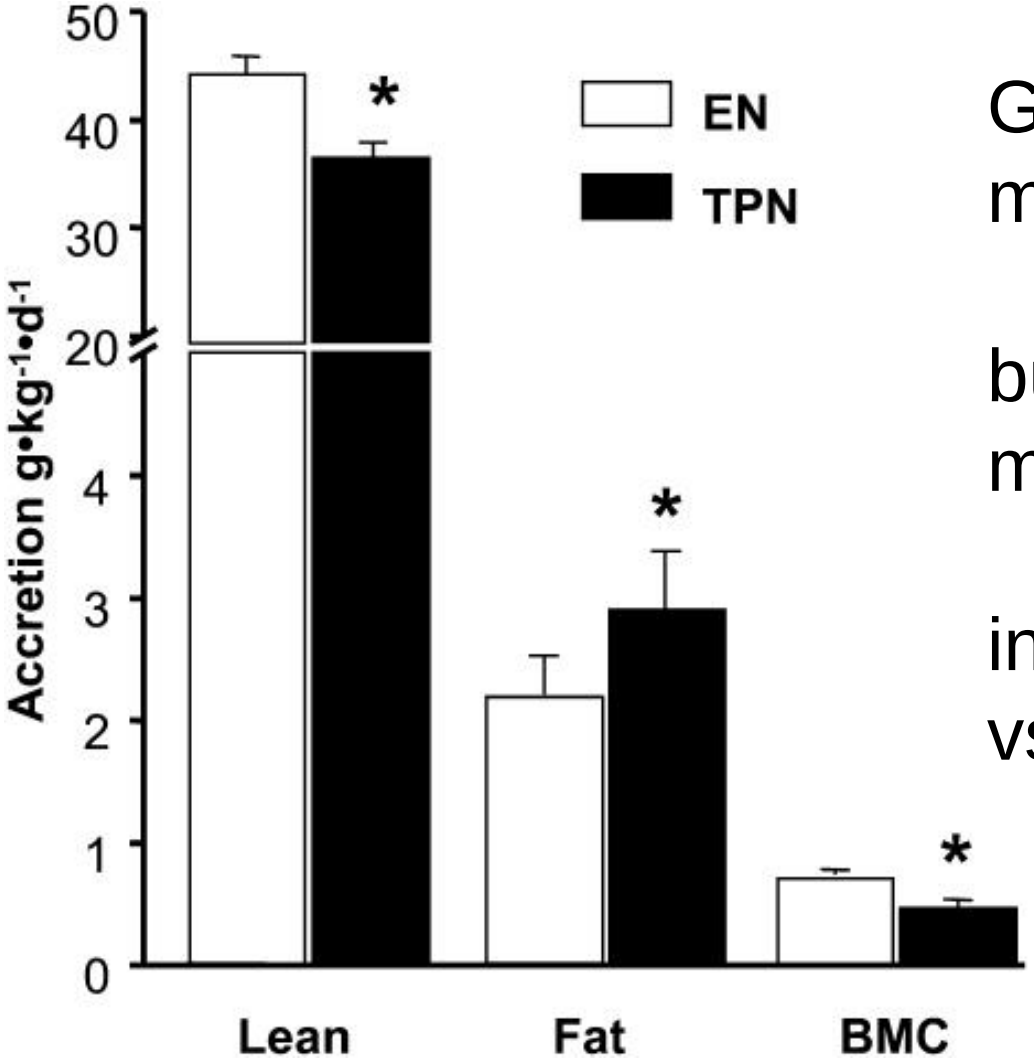
1. Glucose is pumped into the infant at rates and concentrations that are higher than the infant can use.
2. The excess glucose load produces hyperglycemia.
3. Amino acids are provided at rates that are less than needed for normal growth rates.

Recommendations

- Appropriate energy
  - Adjust GIR to maintain normal glucose concentrations
    (3-6 mmol/L [54-108 mg/dL])
  - Essential lipids, not just more calories
    (more DHA, less phytosterols)
- Gestational-age-specific protein intake
  (3-4 g/kg/d at 24-28 weeks, less in later gestation)
- Appropriate supplies/concentrations of amino acids
  (more essential AAs; excess AAs/or protein is not helpful)
- Growth factors (e.g., insulin, IGF-1)
  in response, not infused
- Feed enterally as soon as reasonable and advance as rapidly as tolerated, preferably with mothers milk.

- There still is a lot of research to do to determine optimal amino acid and energy supplies in sick or unstable infants and those who have experienced significant intrauterine and postnatal growth restriction.

Intravenous "TPN" feeding may be essential, but it should not be a substitute for enteral nutrition.



Greater accretion of lean mass and BMC,

but lower accretion of fat mass,

in neonatal pigs fed EN vs. PN over 16 days.

Stoll B, et al. J Nutr 2010;140:2193-2200.

University of Colorado
Anschutz Medical Campus
School of Medicine

Thank you

Children's Hospital Colorado

University of Colorado School of Medicine
Section of Neonatology, Perinatal Research Center, and the Child Maternal Health Program in the Colorado Clinical and Translational Sciences Institute

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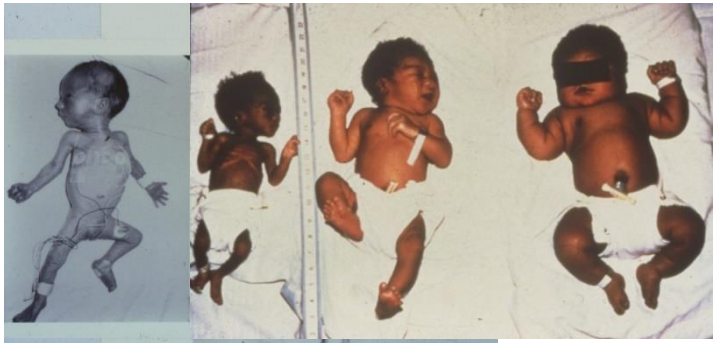
- **Paul Rozance MD**
- **Stephanie Wesolowski PhD**
- **Kendra Hendrickson RD**



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