Creating Feeding Guidelines: Optimizing Growth is Complicated

PQCNC Initiative: Increasing Use of Mother's Milk for the Very Low Birthweight Babies in the Critical Care Centers of North Carolina

Webinar 4/11/2011

L Dunn

Goals of nutritional support for the preterm infant: most are met with use of MBM

- ✓ Optimize short-term outcomes
- Optimize short-term growth
- ✓ Prevent feeding-related morbidities
  - ✓ NEC
  - ✓ Central line complications, including sepsis
  - Osteopenia of prematurity
- ✓ Optimize long-term outcomes

Postnatal growth failure is a major issue for the VLBW infants

- In an NIHCD 1995-6 cohort of VLBW infants, 97% were below 10th % at 36 wks, but only 22% had been born SGA (Lemons, *Peds 2001*;107:e1-e8)

- "the birth of an ELBW infant is a nutritional emergency" (from R. Lawrence's textbook Breastfeeding, 7th ed, 2011, chapter 15 "Premature Infants and Breastfeeding")

Better postnatal growth appears to be associated with better neurological outcome

- Ehrenkranz et al (*Peds 2006*;117:1253-1261) found increased neurological impairment in ELBW infants with poor weight gain (55% if gained only 12 gm/kg/d but 29% if gained 21 gm/kg/d)
- Lucas et al (*BMJ 1998*;317:1481-7) found more CP and lower IQ's in group of <1850 gm infants who had received standard term formula vs group who had received enriched formula
- Latal-Hajnal et al (*J Peds* 2003;143:163-179) found improved neurological outcomes with better postnatal growth (of interest, was not correlated with growth status at birth)

MBM and DBM are considered "insufficient" for the VLBW infants (especially with respect to protein, calcium, phosphorus and some vitamins), but early use of IV protein and human milk fortification may help close the gaps

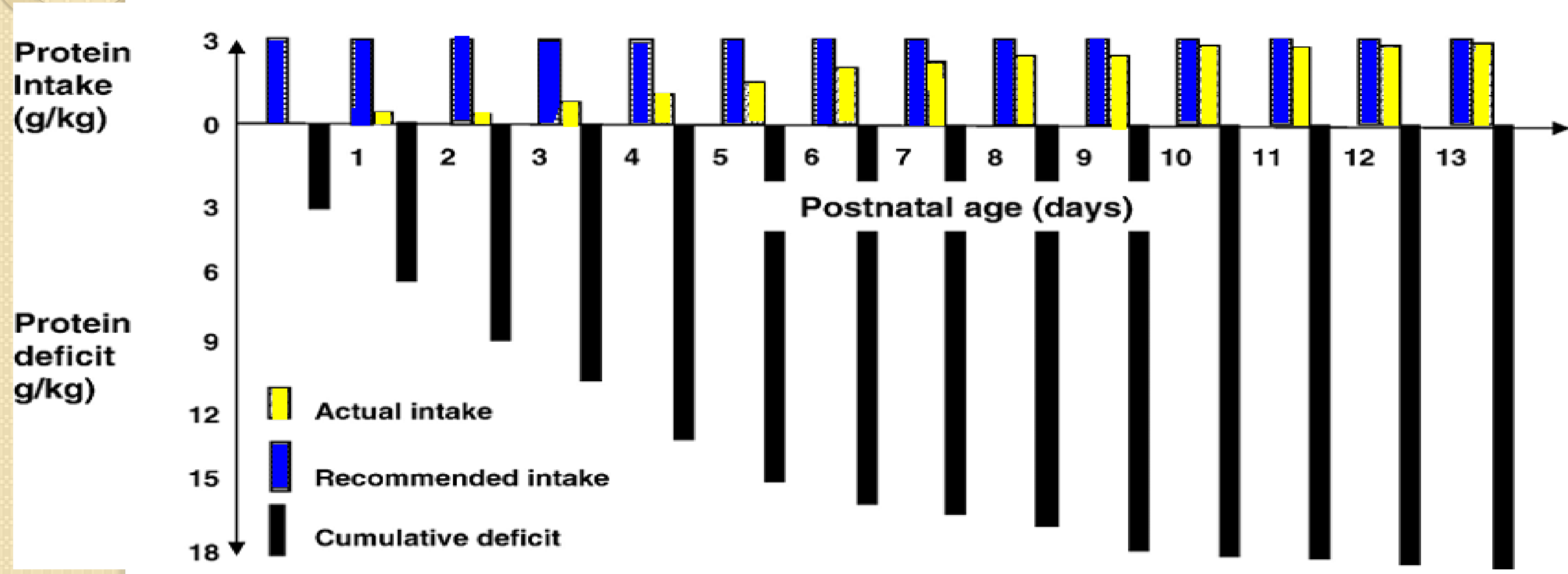
Topics to be addressed today

- Recommendations concerning early parenteral protein/TPN
  - when and how much to start
- Recommendations concerning multicomponent fortification of M/DBM
  - when should fortification begin?
  - how should fortification be achieved?
- What are other things that can be done to address poor weight gain?
- What are the "unknowns" concerning TPN and fortification?

Background re: provision of protein for the VLBW infants

- In utero, the fetus receives more protein than can be incorporated for growth, so the excess is used for energy; glucose is taken up as needed for other metabolic needs
- After delivery we usually give an excess of glucose but usually far insufficient protein
- Studies show that our premature infants quickly develop a protein deficit when standard use of protein is used, and that the deficit usually is not overcome through the hospitalization

Cumulative protein deficit which occurs when protein is started after the first day and then gradually increased



****0.3-0.4 g/kg/day needed over 8 week period to make up this deficit*

Embleton ND. Early Hum Dev 2007;83:831-837

Recommended protein intake

Week of gestation	Parenteral protein intake
24-25 wks	3.75-4 gm/kg/d
27-28	3.5
32	3.2
term	2.8-3

Thureen. Presentation Oct 2,2008, *Neonatal Nutrition, Development and Management* Minneapolis MN and Ziegler. Aggressive nutrition of the VLBW infant, *Clin Perinatology 2002*;29:225.

Weight	Protein intake
Up to 1kg	4-4.5 gm/kg/d
1-1.8	3.5-4
Range (reducing amount if growth sufficient)	3.5-4.5

Agostini. Enteral Nutrient Supply for Preterm infants: Commentary from the European Society for Paed Gastronenterol, Hepatol, and Nutrition Committee on Nutrition. *JPGN 2010*;50:85-91

Change in recommendations for dietary protein requirement

- Recent recommendations are to give more protein, and to start it earlier
- AAP (Pediatric Nutrition Handbook 4th ed 2008)
  - 3.5-4 gm/kg/d
- Consensus recommendations (Tsang et al. Nutrition of the Preterm Infant: Scientific Basis and Practical Guidelines. 2005)
  - <1000 gms 3.8-4.4 gm/kg/d
  - 1000-1500 gms 3.4-4.2 mg/kd/d

Current recommendations for IV protein

- Start with 2-3 gms/kg/d* within the first 24 hours of life
- Increase to 3.5-4 gms/kg/d for the VLBW infants*

*(*use higher end for the ELBW infants)*

From ElHassan 2011
And CPQCC 2008

Early "Aggressive" Parenteral Nutrition

- Should include use of IV lipid, start at 2-3 g/kg/day and increase to doses as high as 3-3.5 gm/kg/d over the first few days of life
- Outcomes of more aggressive TPN use:
  - positive nitrogen balance within 48 hours
  - improved albumin synthesis
  - little azotemia (more info on BUN's later), no metabolic acidosis (normal HCO3), little hyperammonemia
  - lower serum glucose
  - lower incidence of
    - weight <10th percentile at 36 weeks corrected age
    - suboptimal head circumference at 18 months

Thureen et al. Pediatr Res. 2003;53:24-32. Ibrahim et al. J Perinatol 2004;24:482-486. Drechenpohl et al.Pediatrics 2008;122:743-751. Poindexter et al. J Pediatr 2006;148:300-305

Can an aggressive nutritional approach improve outcomes?

- At least 4 studies show that early TPN has ability to decrease postnatal weight loss, and to improve overall weight gain and length, and head circumference at hospital discharge (Dinerstein *J Perinatol 2006*;26:436-42, Wilson *Arch Dis Child FNE 1997*;77:F4-11, Christensen *J Perinatol 2006*;26:37-43, and Valentine *J Perinatol* 2009;29:428-432)

Current recommendations for fortifying breastmilk

- Start when enteral feeds are at 80-100 ml/kg/d
- Use multicomponent fortification
  - Fortifiers contain vitamins, minerals, including calcium and phosphorus, and protein; variable amount of fat and carbohydrate
  - Note: in the past, protein has often fallen below recommended levels (as has fat content) even when milk is "fully fortified"

CPQCC 2008

Options for fortifiers

- Options in the USA are currently undergoing change, and include fortifiers that are the traditional powdered cow-milk derived (Abbott labs), new liquid cow-milk derived (Mead Johnson's is out now, and Abbott plans to roll out theirs in a few months) as well as a relatively new liquid human-milk derived (Prolacta)
- Another option is to use high calorie formula (such as Sim 30)

Cow-milk derived fortification improves growth and bony density

- From Cochrane Database, meta-analysis by Kuschel and Harding (2004)
- >600 babies, 13 RCT's (published from 1986-2000)
- Results:
  - Improved weight gain (2.3 gm/kg/d)
  - Improved length and HC (both increase 0.12 cm/wk)
  - Improved bone mineral content
  - Higher BUN (but none> 20)
  - No adverse effects (such as death, feeding intolerance or NEC) found to be significant
  - However, of note, little long-term follow up

How to choose among fortifiers?

- As noted, in the USA, we are in the midst of changes, with the liquid cow-milk derived form just now being introduced by two companies
- Few head-to-head comparisons have been made
- A big unknown is whether displacing MBM by a fraction will decrease the protective impact of MBM
- Hopefully more research will be available soon
- One head to head trial was recently published…

Sullivan et al. An exclusively human milk-based diet is associated with a lower rate of NEC than a diet of human milk and bovine milk-based products. *J Peds 2010*;156:562-567

- Only article to date to compare the human-milk derived fortifier head to head with cow-milk derived fortifier; unfortunately they supplemented one group with formula, not donor milk
  - Among 11 units, 207 babies were randomized. Avg wt ~900 gms, avg GA ~27 wks, were nearly equally divided among 3 groups: MBM+donor milk+ human-milk derived HMF started at 100 ml/kg/d enteral feeds, MBM+donor milk+human-milk derived HMF started at 40 ml/kg/d enteral feeds, or *MBM+formula+cow-milk derived HMF*

Sullivan et al. An exclusively human milk-based diet is associated with a lower rate of NEC than a diet of human milk and bovine milk-based products. *J Peds 2010*;156:562-567

- results: no difference in time on TPN/length of time with central lines in, weight gain, length of stay, or combined outcome of late-onset sepsis or NEC
- However, medical NEC itself was reduced from 16% (bovine group) vs 6% (human group) and surgical NEC was reduced from 10% to 2%

- *But how to separate out the impact of the fortifier vs the formula??*

Also note impact of powdered fortifier on antibacterial actions of human milk

- Cow-milk derived fortifier containing iron decreased the antibacterial action of human milk (against E coli, S aureus, GBS and E sakazakii)

Chan. Effects of powdered milk fortifiers on the antibacterial actions of human milk. *J Perinatol 2002*;23:620-623.

- However, the same group tested the human-milk derived fortifier (with little iron) and found no decrease in antibacterial action

Chan. Effects of a human milk-derived human milk fortifier on the antibacterial actions of human milk. *Breastfeed Med 2007*;2:205-208.

A bit more about Prolacta: use and costs

- Prolacta is a for-profit milk bank (the only one in the USA; about 14 non-profit milk banks are open in the North America)
- A donor milk product is available from Prolacta
- Several fortifiers available (+4, +6, +8)
- The "+4" fortifier comes as 10 ml in a bottle ready to be mixed with 40 ml of human milk
- But cost is a big factor, and is something hospitals have to struggle with daily…

Ethical dilemma: the human-milk derived fortifier appears preferable, but cost is huge

- Standardized Prolacta donor milk product, $30/oz, vs. HMBANA product (without nutritional analysis), $4/oz
- Estimated cost of different forms of 24 cal breastmilk, 100 ml:
  - MBM+ 4 pkgs HMF/100ml: $6
  - HMBANA DBM+ 4 pkgs HMF/100 ml: $19
  - MBM + Prolacta +4/100 ml: $125
  - Prolacta DBM + Prolacta HMF +4/100 ml: $225
  - MBM + Prolacta +8/100ml: $250
- Estimated cost (per Prolacta estimates) for the Prolacta fortifier per <750 gm baby in our unit was $10,000/baby; even adjusting for the cost of NEC in our unit (5 cases of medical NEC in 5 yrs, and 1 case of surgical NEC) using the product would result in an extra ~$7,000/baby

How to balance costs?

- And, for example, if we estimated the cost to be an extra $10,000 to use in all of our <1500 gms babies here at WakeMed, we would spend about $1.5 million/yr just for the use of the fortifier [to put that in perspective, we use about 300 oz/mo of donor milk, at ~$4/oz, which equals (300 oz x $4.00 x 12mo) about $14,400 total, for the milk alone, for all of these babies combined, for the year]

Beyond the multicomponent fortifier, adding additional enteral protein improves growth as well

- Reminder: requirement for growth estimated (Ziegler) to be 4.3 gm/kg/d for the <1000 gm baby, and 3.2 gm/kg/d for the 1000-1500 gm baby
- Under our present system with the powdered fortifier, fortified breast milk provides ~3.6-3.8 gm/kg/d when fed at 120 kcal/gm/d, EPF and SSC provide 3.6; the new high protein formula (Enfamil) provides`4.2, and the new liquid fortifier (MJ) provides >4
- When we use "added propass" at ¼ tsp/100 ml, we add 0.3 gm/100ml of protein, at ½ tsp/100 ml, we add 0.6 gm/100 ml
- Can improve short-term weight gain, length and head circumference
- May increase BUN
- But plenty of caveats:
  - Most information about protein is from babies fed formula
  - Very little long-term follow up on these babies (no proof that increasing fortification of breast milk leads to better neurological outcome)
- Hopefully the future will bring us more badly-needed information

Adjustable fortification of human milk fed to preterm infants: Does it make a difference?

(Arslanoglu S et al. J Perinatol. 2006;26:614–62)

- Compared protein fortification with human milk fortifier plus bovine whey protein to standard fortification
- Study group received incremental increases in protein
- Average intake of 3.2 g/kg/day compared to 2.9 g/kg/day
- Significant differences
  - Weight gain +3 gm/kg/day
  - Head circumference +0.4 mm/day
- Weight and head circumference gain were significantly ($P<0.05$) correlated with protein intake
- No significant differences between groups in BUN, creatinine, calcium, or phosphorus

Possible ways to prevent suboptimal weight gain

- To help prevent poor weight gain secondary to protein insufficiency, provide sufficient IV protein from first day/hour
- Address techniques that may enhance fat delivery (bolus feeds, short tubing, being sure syringe is empty at end of infusion, trying to avoid separation of fat fortifier components)
- Careful and frequent monitoring is critical (aim for ~15-20 gm/kg/d) and recheck every several days; modify your approach if these guidelines are not being met (Ehrenkranz *Peds 2006* and Uhing *Clinics in Perinatology 2011*)

Preventing suboptimal infant weight gain: helping mother understand how her milk supply can be optimized

- Review mother's pumping routine
- Determine if she is
  - Using a hospital grade breast pump
  - Pumping until all milk is removed
  - Hands on pumping
  - Bringing in all of her milk – not just the first morning collection which is lower in fat/calories (and make sure the nurses are not using only that milk)
  - Inadvertently separating her milk into fore milk and hind milk, and bringing in more fore milk than hind

Meier P, et al. Breastfeeding Medicine, Jun 2006; 1(2): 79-87.
Morton J, et al. J Perinatol. 2009;29:757,

Other ways of troubleshooting poor weight gain

- If weight gain insufficient after infant has been on 160 ml/kg/d of 24 cal milk for a week, insure oldest breast milk (higher in protein) available is being used. May also consider:
  - Hindmilk (higher in fat)
  - Increasing volume to 180-200 ml/kg/d (if infant does not have CLD)
  - Adding 5th pack of HMF
  - Adding more protein (?aim for BUN to be 9-14*)

*Arslanoglu, J Perinat 2006

Troubleshooting poor weight gain, cont'd

- ?possible role of kangaroo care in enhancing weight gain (Cochrane review 2003, Conge-Agudelo 2003)
- ?possible role of physical activity (Schultze, Cochrane review 2009 showed improved weight gain of 2.3 gm/kg/d); possible improvement of bone health, as well…

Prevention of osteopenia of prematurity

- Provide recommended dietary intakes:
  - Calcium 100-220 mg/kg/day
  - Phosphorus 60-140 mg/kg/day
  - Vitamin D 160 – 400 IU

Rigo J et al. Acta Paediatrics.2007;969-974
Moyer-Mileur LJ. Pediatrics 2008;28:432–437.
Kislal F, Dilmen U. Pediatrics International 2008;50:204–207
Wagner C, Greer F. Section on Breastfeeding and Committee on Nutrition. AAP. Pediatrics 2008;122:1142.

- Optimize that provided by parenteral nutrition
  - Computer assisted ordering
  - Calcium/phosphorus solubility curves
  - Cysteine hydrochloride
  - Calcium:phosphorus ratio

Porcelli P et al. J Am Coll Nutr. 1997;16:238.

Using enteral nutrition to prevent osteopenia of prematurity

- Classically was thought to be problem with insufficient phosphorus
- Role of maternal Vit D status may be important for some babies
- Enteral nutrition
  - Start enteral feeds early
  - Start HMF, 4 pks/100ml, @100ml/kg/day
    - Advance to 150ml/kg/day providing estimated calcium of 213mg/kg/day and phosphorus 120 mg/kg/d
  - If fluid restricted, consider 6 pks/100ml
    - Advance to 125-130ml/kg/day providing calcium 250mg/kg/day and phosphorus 140 mg/kg/d

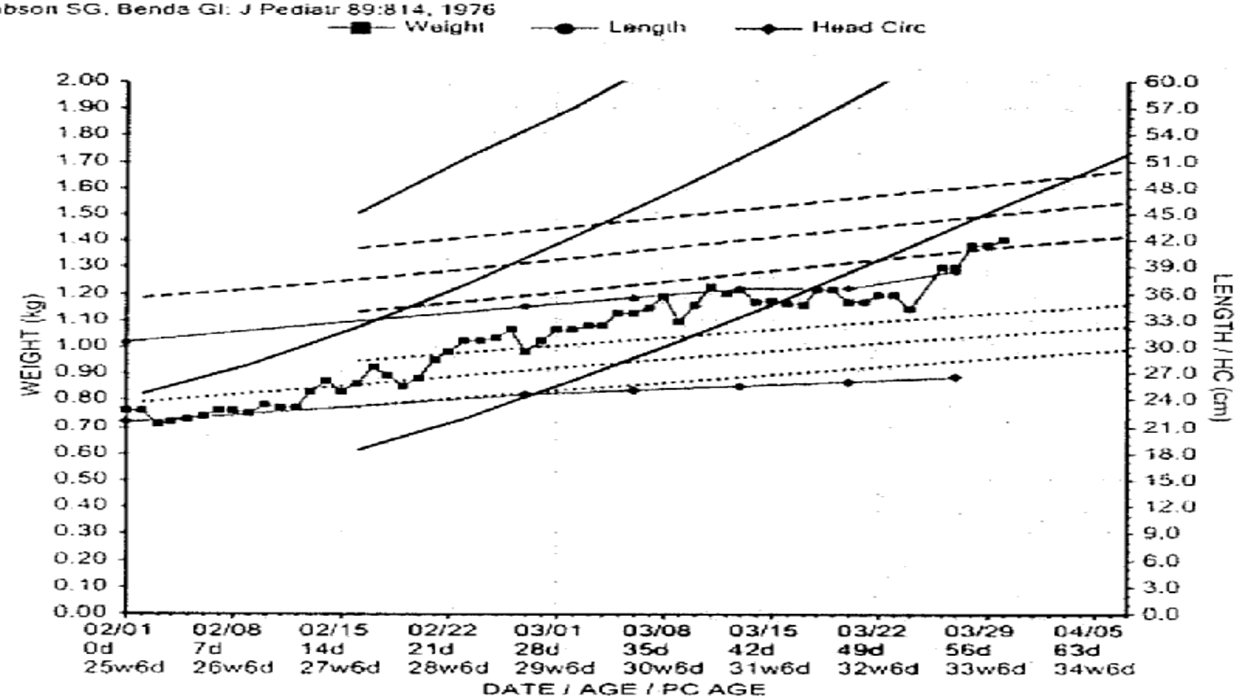
This is what we hope to avoid

WakeMed
Raleigh, NC

[redacted] **GROWTH CHART PAGE 1 OF 1** **03/31/2009**

BIRTH DATE: 2/1/2009
ADMIT DATE: 2/1/2009
CURRENT DATE: 3/31/2009

Postnatal Growth: Mean ± 2 S D.
Babson SG, Benda GI: J Pediatr 89:814, 1976



[redacted] **GROWTH CHART PAGE 1 OF 1** **03/31/2009**

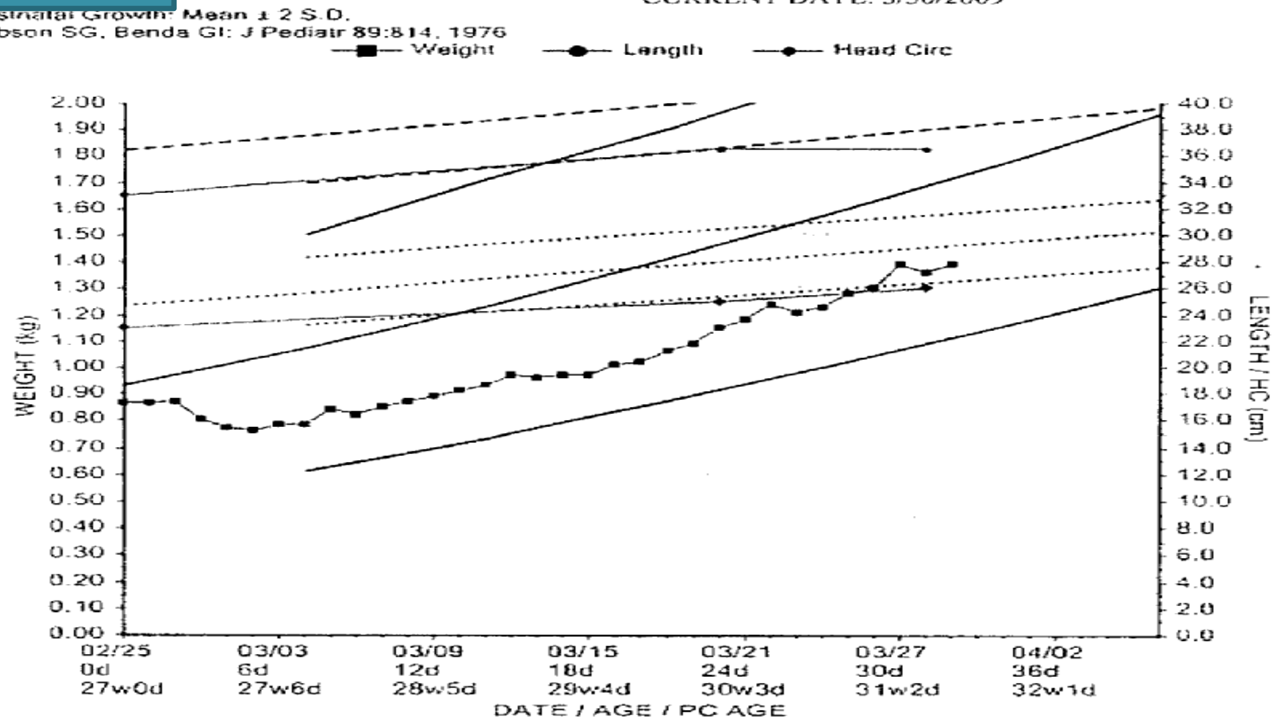
Former 25 and 6/7 wk 760 gm Twin A, fed unfortified MBM until ~3/25

This is looking better

WakeMed
Raleigh, NC

GROWTH CHART PAGE 1 OF 1 03/30/2009

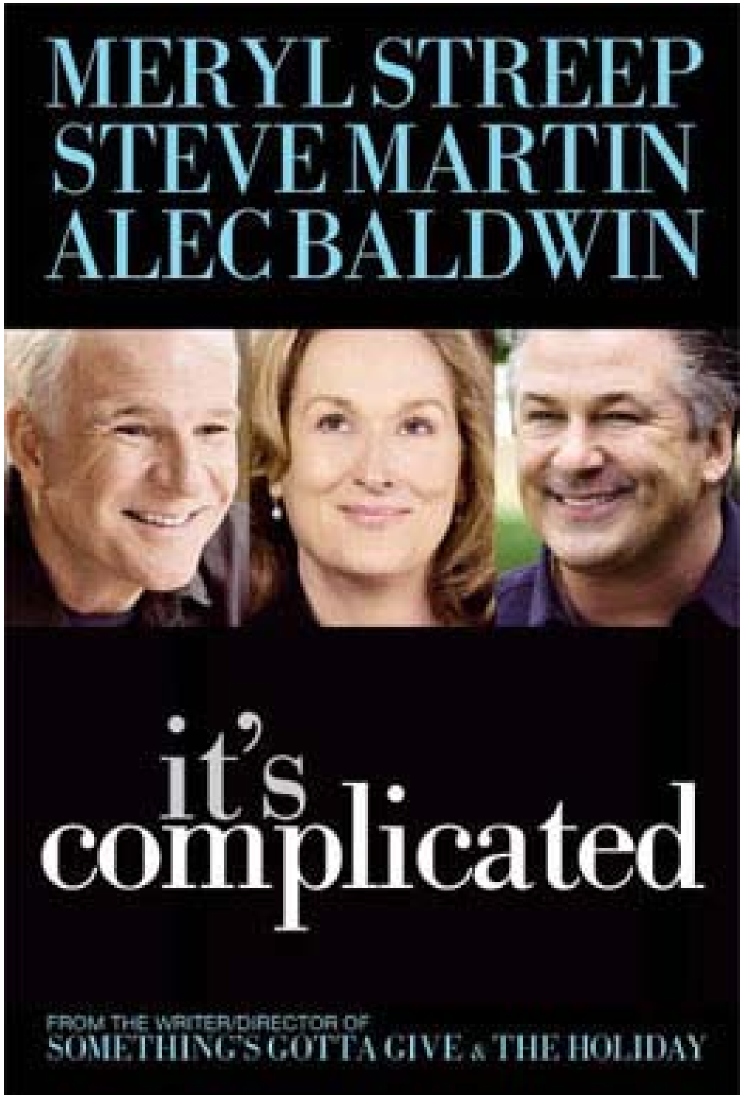
BIRTH DATE: 2/25/2009
ADMIT DATE: 2/25/2009
CURRENT DATE: 3/30/2009



GROWTH CHART PAGE 1 OF 1 03/30/2009

Former 27 wk 865 gm infant,
fed all 24 cal MBM plus PP

But….
"It's Complicated"



Uncertain aspects: what is optimal growth?

- Generally optimal growth is felt to be that equal to the intrauterine growth curve
- However, both hypertension and insulin resistance has been reported in the LBW babies who had rapid catch-up growth after birth (Law, *Circulation 2002* & Singhal, *Lancet 2003*)
- Eriksson et al (*BMJ 1999*;318:427-431) found death from coronary artery disease was increased in LBW infants, especially those who achieved catch-up growth to the 50% or higher by 7 years of age

Information summary from Uhing and Das, Optimizing Growth in the Preterm infant, *Clinics in Perinatology 2009*;36:165-176

If infant received fortified MBM and achieved better postnatal growth, is that associated with better neurological outcome?

- Ehrenkranz et al (*Peds 2006*;117:1253-1261) found increased neurological impairment in ELBW infants with poor weight gain (55% if gained only 12 gm/kg/d but 29% if gained 21 gm/kg/d) (no details of nutritional regimen)
- Lucas et al (*BMJ 1998*;317:1481-7) found more CP and lower IQ's in group of <1850 gm infants who had received standard term formula vs group who had received enriched formula (formula-fed)
- Latal-Hajnal et al (*J Peds* 2003;143:163-179) found improved neurological outcomes with better postnatal growth (no details of nutritional regimen)
- ***Lucas et al. Randomized outcome trial of human milk fortification and developmental outcome in preterm infants. Am J *Clin Nutr 1996*;64:142-151. *Only RCT of fortified breast milk with long-term follow up*. Note: overall, intake of MBM was <50% during hospital stay. MDI scores 106 (fortified) vs 104(unfortified) at 18 mo's not considered significant

And there may be another side of the coin with respect to IV protein

- Clark et al (Effects of two different doses of amino acid supplementation on growth and blood amino acid levels in premature neonates admitted to the intensive care unit: a RCT. *Peds 2007*;120:1286-1296) studied 122 VLBW infants: randomized to low AA (start at 0.5 gm/kg/d and advance to max of 2.5) or start at 1.5 and advance to 3.5
  - Results: significant differences in serum AA levels, raising fear of toxicity

And this month, another article about high amino acid levels

- Blanco (Plasma amino acid concentrations during aggressive nutritional therapy in ELBW infants. *J Peds* 2011;158:543-548) found similarly elevated amino acids in some babies. Half received a standard protocol (starting at 0.5, and advancing by that amount daily). The more-aggressive regimen was to start AA in first 24 hours at 2 gms/kg/d, and to advance by 1 gm/kg/d up to max of 4. Their protocol was to draw serum ammonia levels if BUN was >60, and they would hold amino acid infusions if ammonia was >91umol/L (day 1) or 79 (day 3). 9 babies out of 61 had the elevated BUN levels, 6 of those had the specified high ammonia levels. 8 of the 9 babies with high BUN's were in the aggressive protein group.

- ****There needs to be a balance. We should be cognizant of a possibly negative neurologic effect, with the higher protein levels. Possibly following the protocol re: BUN and ammonia levels above would be reasonable(?).*

Other issues related to neonatal nutrition

- Note: "the influence of fortifiers and other additives in milk has not been tested rigorously for effects on NEC or other gastrointestinal complications" (Hay, 2010)
- Should the IUGR babies have a different feeding regimen? (They seem to be at higher risk for NEC, may not be able to metabolize protein as well)
- Is the current trend of accepting lower oxygen sats and hematocrits going to decrease ability to grow optimally?

Other issues related to neonatal nutrition

- What is the role of shielding TPN from phototherapy? [less oxidation of certain amino acids and vitamins, ?less BPD (Chessex, J Peds 2007) and ?less hypertriglyceridemia (Kashu, Arch Dis Child FNE 2009)]
- Can changing feeding practices around transfusions decrease the NEC related to blood transfusions??
- What about transition home?
- Pre/postbiotics

And other uncertain aspects

- How do you differentiate impact of intrauterine programming, early neonatal nutrition and later childhood nutrition on CV health, and how do you differentiate nutritional impacts vs all the other possible impacts of early birth on brain development?
- (and the list could continue from here……)
- ***Continue to watch nutrition field for other developments, especially as we watch these VLBW infants grow up

Information summary from Uhing and Das, Optimizing Growth in the Preterm infant, *Clinics in Perinatology 2009*;36:165-176

Summary: Mother's milk is best for short and long-term outcomes for the VLBW infant. We are still learning the best way to otherwise support neonatal nutritional needs.

Thanks. Questions/comments?

References

- CPQCC Quality Improvement Toolkit, Nutritional Support of the VLBW Infant, 2008.
- Adamkin. Nutritional management of the very low-birthweight infant. Parts I and II. *NeoReviews 2006*;7:e602-e614.
- ElHassan and Kaiser. Parenteral nutrition in the neonatal intensive care Unit. *NeoReviews 2011*; 12:e130-e140.
- Hay. Strategies of feeding the preterm infant. *Neonatology 2008;94:245-254*
- Martin et al. Nutritional practices and growth velocity in the first month of life in extremely premature infants. *Pediatrics 2009*;124:649-657.
- Uhing and Das, Optimizing growth in the preterm infant. *Clinics in Perinatology 2009*;36:165-176
- NICHD Cochrane Neonatal Collaborative Research Database
  - Kuschel and Harding. Multicomponent fortified human milk for promoting growth in preterm infants (2004)
  - Kuschel and Harding. Protein supplementation of human milk for promoting growth in preterm infants (2000)

Porcelli and Sisk. Increased parenteral amino acid administration to ELBW infants during early postnatal life. *J Ped Gastroenterol Nutr 2002;34:174-9*

- Study from Wake Forest Univ
- VLBW infants received a "modified regimen" of higher aa intakes, up to 4 gm/kg/d. Specifically they received doses as high as 3.3 gm/kg/d of aa by end of wk 1, and 3.8 by end of wk 2
- No increase in acidosis, minimal increase in BUN
- *Better growth from wk 1*

Cow-milk derived fortification improves growth and bony density

Fortified vs Unfortified Human Milk

- > 600 infants; randomized*
- Growth

	Weighted Mean Difference	
Weight gain (g/kg/d)	+ 3.6 [2.7; 4.6]	
Length (cm/wk)	+ 0.12 [0.07; 0.18]	
Head circumference (cm/wk)	+ 0.12 [0.07; 0.16]	
Bone mineral content (mg/cm)	+ 8.3 [3.8; 12.8]	
Nitrogen balance (mg/kg/d)	+ 66 [35; 97]	
BUN (mg/dL)	+16 [8; 24]	
Relative Risk	**Relative Risk**	
Feeding intolerance	2.9 [0.6; 13]	NS
Necrotizing enterocolitis	1.3 [0.7; 2.5]	NS
Death	1.5 [0.7; 3.3]	NS

Kuschel CA & Harding JE 2004 The Cochrane Library

**Some comparisons with partial supplements*

Another researcher, using different methods, found variable impact of fortification on the antibacterial properties of breastmilk

- Quan et al. The effect of nutritional additives on anti-infective factors in human milk. *Clin Peds 1988*:33;235-8)
  - Researchers measured lysozyme activity, IgA, specific IgA to certain E coli serotypes, and E coli growth in frozen human milk, comparing impact of various additives
  - Results: all cow milk based formulas (Sim, Sim Sp Care, Enf, EPF) decreased lysozyme activity by 41-74%, though no differences in total IgA was seen. Fortifier decreased lysozyme by 19%
  - However, only the cow-milk formulas actually enhanced bacterial growth