Impact of Growth on Neonatal Outcomes

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Disclosure Statements
Richard A. Ehrenkranz, MD
I have no relevant financial relationships to disclose or conflicts of interest to resolve.

I will not discuss any unapproved or off-label, experimental or investigational use of a product, drug, or device.

Objectives

● To discuss curves used to monitor postnatal growth of preterm infants, especially extremely preterm (EPT) infants

● To review the data that:
  • postnatal growth reflects the adequacy of nutrient intake
  • growth correlates with neurodevelopmental outcomes

● To recommend the implementation of feeding guidelines

Plotting Serial Anthropometric Measurements on Growth Curves

• Provide an assessment of nutritional status
• Permit comparisons with established norms
• Identify alterations in growth patterns
  ➢ Symmetric vs asymmetric
  ➢ Growth along a percentile vs faltering
  ➢ Growth below the 10th percentile
• Assess response to interventions

Nutritional Management of Preterm Infants: Current Recommendations

To provide nutrients to approximate the rate of growth and composition of weight gain for a normal fetus of the same postmenstrual age and to maintain normal concentrations of nutrients in blood and tissue.

Growth Curves and Postnatal Growth of Preterm Infants

- Controversy exists over feasibility and appropriateness of achieving AAPCON goal.

- Descriptive curves based upon:
  - Intrauterine growth data
  - Postnatal growth data

Yale Estimated Fetal Weight Growth Curve

IU Growth from Live Births at 26-42 Weeks’ Gestation

Lubchenco. Pediatr 1966; 37: 403-408

IU Growth from Live Births at 25-44 Weeks’ Gestation


A New Growth Chart for Preterm Infants


New IU Growth Curves Based on US Data

Limitations of Intrauterine Growth Curves for Monitoring Postnatal Growth

- Curves represent cross-sectional data derived from newborns, not serial measures over time
- Preterm infants may not be “normal”
- Gestational age dating is imprecise
- Curves maybe population specific, and not generalizable
Postnatal Growth of VLBW Infants vs Expected Intrauterine Growth

Postnatal Weight Gain After Very Preterm Birth: A UK Population Study

RCT: Aggressive Nutritional Support in VLBW Infants

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=64)</th>
<th>Control  (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age regain BW</td>
<td>9 d</td>
<td>12 d*</td>
</tr>
<tr>
<td>NEC</td>
<td>8 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>50 %</td>
<td>66 %</td>
</tr>
<tr>
<td>CoNS bacteremia</td>
<td>44 %</td>
<td>56 %</td>
</tr>
<tr>
<td>At d/c or death:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body wt &lt; 10th%</td>
<td>59 %</td>
<td>82 %*</td>
</tr>
<tr>
<td>Length &lt; 10th%</td>
<td>56 %</td>
<td>74 %</td>
</tr>
<tr>
<td>HC &lt; 10th%</td>
<td>14 %</td>
<td>30 %</td>
</tr>
</tbody>
</table>

[* p<0.05]


Early & Aggressive Nutrition Strategy in VLBW Infants:

Historical Control Study

<table>
<thead>
<tr>
<th>Protein</th>
<th>Aggressive (n=117)</th>
<th>Conventional (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 g/kg/d (hrs) to 4.0 g/kg/d</td>
<td>0.5 g/kg/d (d3) to 3.0 g/kg/d</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Aggressive (n=117)</th>
<th>Conventional (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 g/kg/d (24 hrs) to 3.5 g/kg/d</td>
<td>0.5 g/kg/d (d3-4) to 3.0 g/kg/d</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Enteral</th>
<th>Aggressive (n=117)</th>
<th>Conventional (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mL/kg/d HM or PF (d1), ↑ by 10 mL/kg/d x 7 d, then 15-20 mL/kg/d to 180 mL/kg/d</td>
<td>started when stable; advanced per team.</td>
<td></td>
</tr>
</tbody>
</table>


### Neurodevelopmental Outcomes at 18-22 mos by Weight Gain Quartile

- MDI <70
- PDI <70
- Impairment


### Cerebral Palsy at 18-22 mos by Weight Gain Quartile


### Growth Outcomes at 18-22 mos by Weight Gain Quartile

Early Provision of Parenteral AA in ELBW Infants: Growth Outcomes at 36 wks PMA

<table>
<thead>
<tr>
<th></th>
<th>Early (n=182)</th>
<th>Late (n=836)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (gms)</td>
<td>1958 ± 383</td>
<td>1819 ± 320</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Wt &lt;10th %tile</td>
<td>127 (82%)</td>
<td>681 (95%)</td>
<td>4.2 (2.4-7.5)</td>
<td></td>
</tr>
<tr>
<td>Wt &lt;5th %tile</td>
<td>108 (70%)</td>
<td>605 (85%)</td>
<td>2.1 (1.4-3.2)</td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>41.7 ± 2.7</td>
<td>41.0 ± 2.3</td>
<td>0.0108</td>
<td></td>
</tr>
<tr>
<td>HC</td>
<td>30.9 ± 1.8</td>
<td>30.3 ± 1.6</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>


Neurodevelopment at 18-22 mos CA

<table>
<thead>
<tr>
<th></th>
<th>Early (n=182)</th>
<th>Late (n=836)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td># Evaluated</td>
<td>154 (85%)</td>
<td>712 (85%)</td>
<td></td>
</tr>
<tr>
<td>Bayley MDI&lt;70</td>
<td>33%</td>
<td>32%</td>
<td>0.9 (0.6-1.4)</td>
</tr>
<tr>
<td>Bayley PDI&lt;70</td>
<td>17%</td>
<td>19%</td>
<td>1.1 (0.8-1.9)</td>
</tr>
<tr>
<td>Cerebral Palsy (any)</td>
<td>17%</td>
<td>14%</td>
<td>0.6 (0.4-1.0)</td>
</tr>
<tr>
<td>Hearing Disability</td>
<td>3%</td>
<td>3%</td>
<td>1.1 (0.4-3.3)*</td>
</tr>
<tr>
<td>Blindness (L or R)</td>
<td>0%</td>
<td>1%</td>
<td>(p=0.224)*</td>
</tr>
<tr>
<td>NDI</td>
<td>32%</td>
<td>35%</td>
<td>1.0 (0.6-1.5)</td>
</tr>
</tbody>
</table>


First-Wk Protein Intake Are Associated with 18-mos CA Developmental Outcomes in ELBW Infants

- Regression analyses controlling for BW, gender, IVH, BPD, NEC and maternal education demonstrated:
  - Each 1 gm/kg/d increase in protein intake:
    - 8.2-point increase in MDI
    - Accounted for 17% of the variance in MDI
  - Each 10 kcal/kg/d increase in energy intake:
    - 4.6-point increase in MDI
    - Accounted for 18% of the variance in MDI

Intrauterine, Early Neonatal, and Postdischarge Growth & Neurodevelopmental Outcome at 5.4 Yrs in Extremely Preterm Infants After Intensive Nutritional Support


- Study Design: 219 (83%) of 263 surviving VLBW infants born between July 1996-June 1999 were evaluated at about 5 yrs of age with:
  1) standardized neuroexam
  2) Kaufmann Assessment Battery for Children
  3) Gross Motor Function Classification Scale

- All infants received “intensive early nutritional support” that included initiation of parenteral protein (2 g/kg/d) on day 1 and enteral feeds (~16 mL/kg/d) on day 1. Parenteral protein was increased to 3 g/kg/d; enteral feeds by ~16 mL/kg /d.
Contribution of Perinatal Risk Factors on Mental Processing Composite from Multiple Linear Regression Models

<table>
<thead>
<tr>
<th>Parameter (in weight model)</th>
<th>Partial R²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH ≥ 3 vs &lt; 3</td>
<td>0.213</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of MV, ≥ 7 vs &lt; 7 d</td>
<td>0.113</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Measure of weight gain</td>
<td>0.035</td>
<td></td>
</tr>
<tr>
<td>SDS at birth</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>∆SDS (D/C – birth)</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>∆SDS (F/U – D/C)</td>
<td>0.884</td>
<td></td>
</tr>
<tr>
<td>PVL, yes vs no</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>Highest maternal education,</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>lowest vs higher sch deg</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Total R² of model</td>
<td>0.396</td>
<td></td>
</tr>
</tbody>
</table>

Franz, Pediatrics 2009; 123:e101-e109

Infant Growth Before & After Term: Effects on Neurodevelopment in Preterm Infants

- **Design:** Observational study of 613 infants < 33 wks GA born between 4/01-10/05; participants of DINO (DHA for Improvement of Neurodevelopmental Outcome) Trial
  1. Anthropometrics at term, 4, 12, & 18 mos CA
  2. Bayley Scales of Infant Development-II at 18 mos CA
- **Findings:**
  1. Between 1 wk-term, greater wt gain → higher BSID scores
  2. Between 1 wk-term w/ BW < 1250 g, stronger associations w/MDI & PDI
  3. Between term - 4 mos, greater wt gain & linear growth → higher PDI scores
  4. Between 4 – 12 mos, no growth associations with BSID


Neonatal Caloric Intake Influences Preterm Infant Head Growth

- AGA infants calorically deprived (< 85 kcal/kg/d) for > 4 wks (SGA infants for > 2 wks) had HC growth -1 to -2 SD below standard HC growth curves at 12 mos CA; AGA infants also had motor developmental delay at 12 mos CA.
- Early high-energy nutrient intake (> 95 kcal/kg/d) between postnatal days 2-10 by VLBW, SGA infants promoted catch-up HC growth & significantly higher DQ/IQ scores from 6 mos to adulthood, when compared to SGA infants w/o catch-up HC growth.
  - Brandt, J Pediatr 2003; 142:463-468

DQ/IQ (m±sd) of AGA preterm infants compared with SGA HC catch-up group (CU) & group w/o HC catch-up (no-CU) from 6 mos to adulthood. (Brandt, J Pediatr 2003; 142:463-468)
Improving Head Growth in Preterm Infants: A RCT

► Objectives: To explore the relationships between early nutrition, postnatal head growth, quantitative brain MRI, and developmental outcome during the 1st yr of life among infants born < 29 wks gestation.

► Methods: Infants were randomized to hyperalimented or standard parenteral and enteral nutrition. Growth was monitored from birth to 36 wks PMA.

Primary outcome: OFC at 36 wks PMA.

Secondary outcomes: Quantitative MRI at 40 wks PMA; Bayley Scales at 3 & 9 mos post-term.


RCT: Improving Head Growth in Preterm Infants < 29 wks’ GA

<table>
<thead>
<tr>
<th>PN composition</th>
<th>Hyperalimented (n=68)</th>
<th>Control (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal/kg/d)</td>
<td>117</td>
<td>93</td>
</tr>
<tr>
<td>Glucose (g/kg/d)</td>
<td>16.3</td>
<td>13.5</td>
</tr>
<tr>
<td>Protein (g/kg/d)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Fat (g/kg/d)</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Age PN initiated: < 24 hrs

PN advancement: Stepwise from 1 g/kg/d P & F to 4 g/kg/d by d7; Stepwise from 1 g/kg/d P & F to 3 g/kg/d by d5

Enteral Nutrition: EBM, preferably w/in 48 hrs; ↑ by 6-12 mL/d


Clinical, Nutritional & Growth Outcomes of All Survivors

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=59)</th>
<th>Control (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to regain BW</td>
<td>10.3 (6.1)*</td>
<td>13.9 (6.3)**</td>
</tr>
<tr>
<td>Median days on PN</td>
<td>17 (12)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Median days to FEN</td>
<td>19 (11)</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Median # sepsis evts/pt</td>
<td>2 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Oxygen @ 36 wks PMA</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>NEC</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Energy intake @ 4 wks</td>
<td>2766 (233)</td>
<td>2621 (191)**</td>
</tr>
<tr>
<td>Protein intake @ 4 wks</td>
<td>73 (7)</td>
<td>64 (9)**</td>
</tr>
<tr>
<td>OFC @ 36 wks (cm)</td>
<td>31.1 (1.5)</td>
<td>31.4 (1.3)</td>
</tr>
<tr>
<td>Length @ 36 wks (cm)</td>
<td>42.9 (2.3)</td>
<td>42.4 (2.1)</td>
</tr>
<tr>
<td>Weight @ 36 wks (g)</td>
<td>2136 (245)</td>
<td>2090 (293)</td>
</tr>
</tbody>
</table>

*Mean (sd); **p<0.01; ***p<0.001


Improving Head Growth in Preterm Infants: Results

► After pooling the study groups, significant correlations existed between:
  - Energy intake & energy deficit during the first 28 d and:
    - TBV @ 40 wks PMA
    - MDI & PDI @ 3 mos post-term, but not 9 mos post-term
  - Anthropometrics @ 36 wks PMA and TBV & CBV @ 40 wks PMA
  - Weight @ 36 wks PMA and both mental and motor outcomes during year 1


Poor Linear Growth Velocity & 2 Yr Neurodevelopmental Outcomes in VLBW Infants

Cognitive scores at 24 mos CA:
  - Not associated with WZ at any time points
  - Associated with HCZ at birth and at 4 and 24 mos CA
  - Associated with LZ at 4 and 12 mos CA

Objectives

- To discuss curves used to monitor postnatal growth of preterm infants, especially extremely preterm (EPT) infants
- To review the data that:
  - postnatal growth reflects the adequacy of nutrient intake
  - growth correlates with neurodevelopmental outcomes
- To recommend the implementation of feeding guidelines

Implement Feeding Guidelines to Minimize Interruption of Antenatal Nutritional Support

- Feeding guidelines should include:
  - “Consensus” early PN and EN evidence-based strategies (ie, potentially better practices)
  - Standardized plan to manage “feeding intolerance”
  - Strategy to maintain steady rate of postnatal growth, adjusting nutritional support if growth parameters not met

Stages of Nutritional Support After Birth of Extremely Preterm Infants

- Initiation
- Transition to full enteral nutrition (FEN)
- Maintenance of steady growth rate on FEN in the NICU
- Post-Discharge nutrition

Stages of Nutritional Support: Initiation

- Target GIR ~ 6 mg glucose/kg/min
- Early initiation of parenteral AA
  - Start within hrs of birth
  - Provide as a “To Deliver” amount
  - 1.5 g/kg/d (minimum)
- Total Fluid for first 24 hrs to provide 80-100 mL/kg/d
  - 50 mL/kg/d of a “starter” (“vanilla”, off-hrs”) PN
  - 30-50 mL/kg/d of glucose, minimal electrolyte soln

Off-Hours TPN

- Glucose 10 mg/dL (D10W)
- Protein (amino acids) 6.0 g/dL
- Minimal electrolytes
- Ca++ 100 mg/dL
- No vitamins, minerals, lipids
- @ 50mL/kg/d: GIR is 3.5 mg/kg/min, protein delivered is 3.0 g/kg/d, & energy delivered is 23 kcal/kg/d

Stages of Nutritional Support: Transition to Full Enteral Nutrition

- Optimize parenteral nutrition (PN)
  - Increase protein intake to ~ 4 g/kg/d
    - Daily increases of 0.5-1.0 g/kg/d
  - Increase GIR to ~ 10 mg/kg/min during first week of life
  - Initiate IFE within 24 hrs of birth
    - Start with at least 0.5 g/kg/d
    - ↑ by 0.5-1.0 g/kg/d to ~ 3.0 g/kg/d
  - Increase % Total Daily Fluids (TDF) as PN over 1st 3-4 days of life
Stages of Nutritional Support:

**Transition to Full Enteral Nutrition**
- Initiate Minimal Enteral Nutrition [(MEN); trophic feeds, gi stim feeds]
  - Start within first 24 - 96 hrs of age
    - Colostrum, if possible
  - Select duration of MEN
    - 24 hrs vs several days
  - Select volume of MEN
    - ~ 10% total daily flud intake (~ 12 mL/kg/d)
  - Select rate of advancement to FEN
    - ~12 mL/kg/d
    - Fortify HM @ ~ 100 mL/kg/d

**Maintenance of Growth on FEN**
- Monitor growth
  - Weight gain ~20 gm/kg/d (over 5-7 days)
  - Length ~ 1 cm/wk
  - HC ~ 1 cm/wk
- Identify causes of decreased rates of growth
  - Energy needs > energy intake
    - Fluid restriction (eg, BPD)
    - Malabsorption
    - ↓ intake during transition to nipple feedings
  - ↓ protein content of fortified MOM (or DM)
- Maintain adequate energy & protein intakes
  - Energy intake ~ 120 kcal/kg/d (minimum)
  - Protein intake : ~ 4.0 gm/kg/d < 30 wks PMA [P/E=3.3]
    - ~ 3.5 gm/kg/d > 30- 36 wks PMA [P/E=2.9]

**Post-Discharge Nutrition**
- Special nutritional requirements persist after D/C
  - Fortified HM
  - Nutrient-enriched post-D/C formula
- Monitor growth with WHO growth curves from term CA to 24 mos CA

**Implementation of Feeding Guidelines Leads to Improved Outcomes, including:**
- BW regained sooner
- FEN achieved sooner (reduced need for PN)
- Cumulative energy & protein deficits reduced
- Decreased rates of late-onset infection & NEC
- Improved anthropometrics at 36 wks PMA and at discharge (eg, fewer infants < 10th %tile
- Mediation of severity of illness
- Reduction of hospital stay

**Summary and Conclusions**
- Extraceuterine growth restriction (EUGR) may be unavoidable for many EPT infants.
- Since postnatal growth reflects nutrient adequacy, growth must be monitored.
- Implementation of evidence-based feeding guidelines leads to improved outcomes.
- Postnatal growth is correlated with growth and neurodevelopmental outcomes in early childhood.