Neonatal Nutrition, Growth and Neurodevelopment

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Objectives

• Influence of growth and nutrition on later neurodevelopmental outcomes in various populations
  – SGA vs AGA and Term vs Preterm
• Potential trade-offs to accelerated growth in various populations
• Measures/Methods of “growth” monitoring in neonates
  – Weight gain, linear growth, body composition

Brain Development through Term Gestation

Brain Development throughout Infancy and Childhood

Thompson & Nelson, 2001

• Early life experiences have long-term effects on many body systems
• Strong evidence to support that suboptimal in-utero growth leads to increase risk of later metabolic disease in certain populations
Rapid Infant Growth

Neurocognitive Development

Obesity, Metabolic Syndrome Risk

Preterm Infants Undergo Postnatal Growth Failure

- Postnatal growth failure is common among VLBW infants and they frequently are unable to recover prior to discharge.
- In 2010, 79% of VLBW remain below the 10th percentile at 36 weeks — improved from 97% in 2001.

Body composition in preterm infants at term equivalent age in MINNOWS (Minnesota Infant Nutrition, Neurodevelopment, and Obesity Study)

<table>
<thead>
<tr>
<th></th>
<th>Preterm</th>
<th>Term</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>3.65 (0.13)</td>
<td>3.98 (0.06)</td>
<td>0.04</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>51.17 (0.46)</td>
<td>52.74 (0.25)</td>
<td>0.003</td>
</tr>
<tr>
<td>Head Circumference (cm)</td>
<td>35.73 (0.22)</td>
<td>36.74 (0.17)</td>
<td>0.8</td>
</tr>
<tr>
<td>Fat Free Mass (kg)</td>
<td>2.97 (0.10)</td>
<td>3.29 (0.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>0.68 (0.03)</td>
<td>0.91 (0.02)</td>
<td>0.02</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>18.69 (0.26)</td>
<td>15.15 (0.46)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Published in Pediatrics 2012

• The American Academy of Pediatrics (AAP) recommends that preterm infants’ growth duplicates fetal growth rates and that their body composition replicates in utero body composition, through very aggressive nutritional support.

Linear Growth in VLBW infants

Body composition in preterm infants at term equivalent age in MINNOWS (Minnesota Infant Nutrition, Neurodevelopment, and Obesity Study)

- At term equivalent age, preterm infants had:
  - Higher % fat (mean difference, 3%; p = 0.03)
  - Lower fat mass (mean difference, 50 g; p = 0.03)
  - Lower fat-free mass (mean difference, 460 g; p = 0.0001)

Published in Pediatrics 2012

Preterm Birth and Body Composition at Term Equivalent Age: A Systematic Review and Meta-analysis

abstract

BACKGROUND AND OBJECTIVES: Evidence from prior preterm infants who are significantly lighter and shorter on testing their term equivalent age (TEA) than those with higher gestational age and birth weight. We validated a systematic review to assess the body composition at term equivalent age post term premature infants.

METHODS: We searched clinicaltrials.gov, PubMed, and Google Scholar for studies published from 1990 to 2012 that compared body composition at term equivalent age post term premature infants. We conducted a systematic review to assess the effect of preterm lab compositions.

CONCLUSIONS: We identified 17 studies that compared body composition at term equivalent age post term premature infants. The studies included 1,067 preterm infants and 1,383 term infants. The studies were divided into two groups: those that used ultrasound to assess body composition and those that used magnetic resonance imaging.

- The ultrasound group included 9 studies that compared body composition at term equivalent age post term premature infants. The studies included 639 preterm infants and 781 term infants. The studies were divided into two groups: those that used ultrasound to assess body composition and those that used magnetic resonance imaging.

- The ultrasound group included 8 studies that compared body composition at term equivalent age post term premature infants. The studies included 428 preterm infants and 602 term infants. The studies were divided into two groups: those that used ultrasound to assess body composition and those that used magnetic resonance imaging.
Greater Postnatal Weight Gain Benefits Neurodevelopment in Premature Infants

- Any Neurodevelopmental Impairment
- Bayley Mental Development Index <70
- Psychomotor Development Index <70
- Cerebral Palsy

![Graph showing quartiles and outcomes](image)

Ehrenkranz et al., Pediatrics, 2006

**Growth and Neurodevelopment**

- **Birth to Term**: HC, Weight and BMI gains improved 18 month neurodevelopmental scores
- **Term to 4 months**: Weight gain and Linear growth improved 18 month neurodevelopmental scores
- **Linear growth improved IQ at 8 and 18 years as well**

<table>
<thead>
<tr>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent with Outcome at 18 mos</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing quartiles and outcomes](image)

**Analysis of Pattern Reversal VEP data**

![Graph showing VEP data](image)

**Correlation between body composition and VEP latency**

<table>
<thead>
<tr>
<th>Body Composition</th>
<th>Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Discharge</td>
<td>p=0.32</td>
</tr>
<tr>
<td>4 months CA</td>
<td>p=0.2</td>
</tr>
<tr>
<td>Fat Mass</td>
<td></td>
</tr>
<tr>
<td>Hospital Discharge</td>
<td>p=0.77</td>
</tr>
<tr>
<td>4 months CA</td>
<td>p=0.09</td>
</tr>
<tr>
<td>Fat-free Mass</td>
<td></td>
</tr>
<tr>
<td>Hospital Discharge</td>
<td>p=0.02</td>
</tr>
<tr>
<td>4 months CA</td>
<td>p=0.005</td>
</tr>
</tbody>
</table>

**VEP**

- Visual evoked potentials (VEP) are EEG's that are time-locked to a specific visual stimulus
- Represent the brain's response to the visual stimulus
- Changes in VEP can be used to reflect visual pathway development
**Speed of Processing**

Figure 2. Overlaid EEG segments from two participants highlighting the difference in timing of the P20 wave peak between individuals
- Infant with higher FFM at both visits
- Infant with lower FFM at both visits

**Birth to Term FFM gains and Neurodevelopment**

- Increased FFM gains = Improved motor and cognitive scores
- Increased FM gains did not improve scores


**Early Nutrition Improves Short AND Long Term Growth**

- Increased inpatient protein intake = higher discharge weight and FFM
- Increased caloric intake = Increased FFM at term and 4 months and increased length to 24 months

Ramel et al. JPEN 2011 and Ramel et al. Neonatology 2012

**Early Nutrition in Preterm Infants**

- Increased protein and energy during 1st week of life improved 18 month neurodevelopmental scores
  - ↑ 10kcal/kg/day = ↑ 4.6 MDI points
  - ↑ 1g protein/kg/day = ↑ 8.2 MDI points

- Increased lipid intake in first 14 days is associated with improved DQ at 1 year of age


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The Effect of Early Human Diet on Caudate Volumes and IQ


effects

n=76
• Standard nutrient – term formula
• Un-supplemented DEBM
• High nutrient group
• Neurologically normal at 8y
• WISC III or WAIS-R
• MRI (1.5T) – T1 images – brain volume & segmentation

Post-Term Supplementation
• Few studies have evaluated the influence of post-discharge nutrition on neurodevelopment

Post-Term Supplementation
• Multiple Cochrane reviews:
  – preterm formula and fortified breast milk after discharge from the NICU improve growth, but not enough evidence for neurodevelopment

Metabolic Risk in Preterm Infants?
• Reduced insulin sensitivity
• Increased risk to develop type II diabetes
• Elevated blood pressure and resting heart rate
• Increased low-density lipoprotein
• Higher truncal fat

Meta-analysis of 10 observational studies (Preterm vs Term SBP)
• Childhood BP ~2.5 mmHg higher in preterm
• Twice as likely to be hypertensive as adults
Metabolic risk is real for preterm infants.... is it due to rapid growth or excess nutrition??

Growth and Metabolic Risk

- Early differences in body composition resolve
- Multiple studies revealing no association between early growth and later HTN, lipid profiles and insulin sensitivity
- Increased BMI and weight gain in first 1-2 years post-term associated with obesity in childhood
- Childhood growth (>18 months) has shown small associations with metabolic syndrome

More study needed on early growth
- Early aggressive nutrition
- Avoid early growth restriction and need for catch-up growth
- Monitor proportionality and linear growth and potentially body composition

Small for Gestational Age Term Infants

- Rapid growth in weight and length in the first months after birth
- Most catch up to peers by 6-12 months
- Poorer neurodevelopmental outcomes than AGA term infants
- More prone to later metabolic disease

How much weight gain is optimal?

Infant weight gain in IUGR infants: BMI and IQ at 7 years

National Collaborative Perinatal Project Data

Pylipow et al., 2008, J. Peds.
Fortification for SGA Term Infants

- Increased calories (68 vs 72 kcals/100 mls) and protein (+0.4 g/100 mls)
- Given for 9 months
- Improved length and OFC gains at 9 and 18 months
- Similar IQ scores at 18 months (MDI 88.6 vs 87) and PDI (90.4 vs 90.7)
- Control BF group with much improved scores (MDI 99.5 and PDI 96.5)
- 9 month DQ actually worse in fortified group

Later Metabolic Outcomes

- Several studies linking rapid weight gain in first 4 months to increased BMI, higher BP and insulin resistance at school age/adolescence
- Body composition and cardiometabolic risk factors assessed at follow-up (6-8 years of age)
- Fat Mass
  - Standard: 2.0 kg
  - Enriched: 2.7 (p=0.04)
- FFM
  - Standard: 19.3
  - Nutrient: 19.8 (p=0.02)
- Blood Pressure
  - Standard: 61.3
  - Enriched: 64.5 (p=0.02)

AGA Healthy Term Infants

- No positive association between rapid weight gain and IQ at 49 months or 8 years
- No linear association between weight gain or linear growth and IQ

Healthy AGA Term Infants

- US cohort of ~900 infants
- Neither weight gain from birth to 8 weeks nor from 8 weeks to 6 months was related to cognition at age 3 years (or 7 years-unpublished).

Metabolic Risk In Term Infants

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Definitions of Growth

• Weight Gain
• Head Circumference
• Linear Growth
• Weight for Length Measures
  – Body Mass Index (Weight/Length²)
  – Ponderal Index (Weight/Length)

Can BMI accurately predict adiposity in newborns?

• BMI z-score is associated with %BF
• Association with BMI (W/L²) is stronger than with Ponderal Index (W/L)
• Both BMI and PI are poor predictors of adiposity at birth

Body Composition Measurement

• DEXA
• MRI
• Air Displacement Plethysmography
• Anthropometric Measures
• Isotope Dilution
• Bioelectrical Impedance Analysis

Dual energy x-ray absorptiometry (DXA)
Two 6 month-old girls with identical BMI but different body composition

Magnetic Resonance imaging (MRI)

• Infant ADP
  – “Pea Pod” (COSMED, Inc.)
  – Released in 2005
  – Validated for infants 1 – 8 kg
  – Test Chamber kept at 30°C
  – Test involves:
    • Length
    • GA, sex, birth date information
    • Infant unclothed
    • High precision body weight
    • 2 minute body volume test

• Air displacement plethysmography (ADP)
  – Assesses body volume
  – Mass/Volume = Density
  – Density of fat is a constant
  – Density of fat-free mass is variable by age and is estimated
  – Prediction equation relates mass, and these densities to yield:
    • Fat Mass
    • Fat-free Mass
    • Percent Body Fat

Advantages of ADP for Preterm Infant Body Composition Measurement

• Highly reliable (ICC >0.95)
• Validated against gold standard methods
• More Rapid than DXA, MRI, dilution methods
• Lower cost than DXA and MRI
• Does not require highly trained technician to operate
• Does not expose to radiation or require sedation
• Well-tolerated by infants
• Has extensions for older infants and young children 2-6 years, and for children and adults 6 and above
• Growth curves developed from live-born infants are used as standards for determining the **adequacy** of weight gain and linear growth.
  – Weight/Length and BMI
  – Normative body composition **along with** a body composition tool will allow for monitoring of **quality** of weight gain.
  – Term curves now exist
  – Preterm in preparation

Summary
• **Infant growth** must **not** be defined as weight gain alone!
• Different Populations = Different goals, risks and benefits
• Amongst preterm infants → early rapid growth is beneficial
  – More work on timing of interventions and types of nutritional alterations
  – Non-nutritional factors

Summary
• Term SGA infants → early growth may increase later metabolic risk without cognitive benefit.
• Term AGA infants → need closer growth monitoring to determine later risk
  – Further work into ideal formulas if breast milk is not available

Thanks!!
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