HUMAN MILK FOR PRETERM INFANTS: ONE SIZE FITS ALL?

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Florida Neonatal Neurologic Network, 2017
Disclosures

- Consultant: Nestle

- Grant Support: Sigma Tau, Chiesi, Duke [NIH]
Objectives

• Scope of the problem
• Rationale for aggressive nutrition
• Benefits of human milk
• Limitations of human milk
• Fortification of human milk
• Outcomes of interest
Introduction

• Rate of prematurity still high in the United States
• Increasing survival of very low birth weight infants
• Overriding attention to cardio-respiratory problems
• “Adjunctive” needs often not addressed: nutrition
CDC Data, NCHS 2014

- Infants born less than 2500g: 318,847
- Percent LBW: 8.00
- Percent VLBW: 1.40
- Percent preterm: 9.57
Low Birthweight

• Important public health indicator
• Not a proxy for maternal or perinatal health outcomes
• Globally, it is measure of long-term maternal malnutrition, ill health, poor pregnancy health care
• Low birth weight may not be the best indicator and a broader definition of the outcome of pregnancy outcome is needed
• Cut-off of 2500g may not be appropriate in all settings: for e.g., in some countries with a high incidence of low birth weight do not have high mortality rates [Sri Lanka]

Intergenerational cycle of growth failure

- Child growth failure
- Early pregnancy
- Low weight and height in teenagers
- Small adult woman
- Low-birth weight infant

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Goals and Requirements

- Optimal nutritional goal is to duplicate normal in utero fetal growth rates
- *Should have no negative impact on growth and development*
- * Achieve maximal appropriate growth without adverse effects*
- In reality, extrauterine growth restriction is almost universal in small premature infants
- Growth restriction or failure associated with adverse outcomes: neurocognitive effects and chronic lung disease
- Accelerated growth associated with insulin resistance, cardiovascular disease

AAP 2008; Ehrenkranz et al., 1999; Morley et al., 1999; Singhal et al., 2003; Singhal, Cole and Lucas 2001; Singhal et al., 2004
Rationale for aggressive nutrition

Last Trimester

Active amino acid transport

Calcium, Phosphorus, Magnesium, Iron, Lipid transfer present; DHA transported

Glucose, facilitated diffusion

Delivery of premature infant

Higher energy expenditure

Inadequate protein and energy intake

Lipid and glucose exceed in utero

Amino acid lower than in utero

Negative Nitrogen Balance
Extremely Low Birth Weight Infants Grow Poorly

Average body weight compared to intrauterine growth

Ehrenkranz, Pediatrics, 1999
Average GV for infants weighing 501 to 1500 g, 2000 to 2013.
Percentage of infants weighing 501 to 1500 g who were discharged below the third or 10th percentiles of the Fenton growth chart, 2000 to 2013.
Weight gain patterns 23-25 weeks

Fenton et al., BMC Pediatrics 2013, 13:92
Growth Quartiles and Outcomes

Ehrenkranz et al., Pediatrics 2006
Human Milk and the Premature Infant

- Late onset sepsis
- Necrotizing enterocolitis
- Neurocognitive adverse outcomes
  - ?VLBW infants
- Retinopathy of Prematurity
- ?Bronchopulmonary dysplasia
- Feeding intolerance
- Metabolic syndrome
- Insulin resistance
- Lower blood pressure and lower low-density lipoproteins

Figure 2: Beneficial Effects of Human Milk Oligosaccharides on Neonatal Intestinal Development

- Promote establishment of beneficial microbiota
- Protect against infection
- Help compensate for developmental immaturity of the intestine
- Promote intestinal adaptation to extrauterine environment

Adapted from reference 66.
Limitations of Human Milk

• Nutrients
  – Protein, energy, calcium, phosphorus, iron, vitamins, sodium, zinc

• Supply
  – Reduced supply, maternal stress, biological

• Delivery
  – Restriction of volumes
  – Inappropriate fortification [donor or mothers own milk]
## Nutrient Recommendations

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Koletzko¹</th>
<th>ESPGHAN²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid, mL/kg/day</td>
<td>135-200</td>
<td>135-200</td>
</tr>
<tr>
<td>Energy, Kcal/kg/day</td>
<td>110-135</td>
<td>110-135</td>
</tr>
<tr>
<td>Protein, g/kg/day</td>
<td>3.5 -4.5</td>
<td>4-4.5 (&lt;1 kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.5-4 (1-1.8 kg)</td>
</tr>
<tr>
<td>Lipids, g/kg/day</td>
<td>4.8-6.6</td>
<td>4.8-6.6 (&lt;40% MCT)</td>
</tr>
<tr>
<td>Calcium, mg/kg/day</td>
<td>120-200</td>
<td>120-140</td>
</tr>
<tr>
<td>Phosphate, mg/kg/day</td>
<td>60-140</td>
<td>60-90</td>
</tr>
<tr>
<td>Vitamin D, IU/day</td>
<td>400-1000</td>
<td>800-1000</td>
</tr>
</tbody>
</table>

MCT=medium-chain triglyceride.
# Growth Expectations

<table>
<thead>
<tr>
<th></th>
<th>500-700g</th>
<th>700-900g</th>
<th>900-1200g</th>
<th>1200-1500g</th>
</tr>
</thead>
<tbody>
<tr>
<td>g/kg/d, fetal</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>g/kg/d, protein intake</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Kcal/kg/d, energy intake</td>
<td>105</td>
<td>118</td>
<td>119</td>
<td>127</td>
</tr>
</tbody>
</table>

Ziegler 2011
## Macronutrient Composition

<table>
<thead>
<tr>
<th></th>
<th>Protein, g/dL (mean)</th>
<th>Energy, kcal/dL (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term milk</td>
<td>0.9-1.5 (1.2)</td>
<td>57-83 (70)</td>
</tr>
<tr>
<td>Donor milk</td>
<td>0.6-1.4 (0.9)</td>
<td>50-115 (67)</td>
</tr>
<tr>
<td>Preterm milk, &lt;29 wks</td>
<td>1.3-3.3 (2.2)</td>
<td>61-94 (78)</td>
</tr>
<tr>
<td>Preterm milk, 32-33 wks</td>
<td>1.3-2.5 (1.9)</td>
<td>64-89 (77)</td>
</tr>
<tr>
<td>Preterm, donor milk</td>
<td>0.8-1.9 (1.4)</td>
<td>53-87 (70)</td>
</tr>
</tbody>
</table>

Feeding Practices

- Colostrum swabbing
- Human Milk, mother’s preferred
- Donor human milk
- Fortify
- Caution in abrupt cessation of amino acids
- Ideal fortification would be analysis + modular fortification
Fortification

- Protein content of human milk declines with duration of lactation
- Routine fortification and a low protein intake from human milk is the main cause of postnatal growth restriction
- Problem is worsened with donor human milk
- Strategies to improve nutritional status
  - Measure protein concentration and target fortification
  - Fortify based on BUN [in the absence of renal dysfunction, BUN is a sensitive indicator of protein sufficiency]
  - Blind fortification
Fortifiers Available

• Powder human milk fortifiers
• Liquid human milk fortifiers
  – Casein hydrolysate
  – Whey hydrolysate
• Human milk-based fortifiers
• Human milk cream
  – 25% fat, 2.5 kcal/mL
## Comparison of 3 Fortifiers

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Acidified Liquid Human Milk Fortifier (HMF 1)</th>
<th>Human Milk Fortifier Extensively Hydrolyzed Protein Concentrated Liquid (HMF 2)</th>
<th>Human Milk Fortifier (HMF 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kcal/oz.</td>
<td>115-130 kcal/kg</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Protein, g/100 calories</td>
<td>4-4.5 g/kg*</td>
<td>4 *(4.8)</td>
<td>3.58 **(4)</td>
</tr>
<tr>
<td>Calcium, mg/100 calories</td>
<td>120-200 mg/kg</td>
<td>145 (174)</td>
<td>152 (182)</td>
</tr>
<tr>
<td>Phosphorus, mg/100 calories</td>
<td>60-140 mg/kg</td>
<td>80 (96)</td>
<td>85 (102)</td>
</tr>
<tr>
<td>Iron, mg/100 calories</td>
<td>4-6 mg/kg</td>
<td>1.9 (2.3)</td>
<td>0.6 (0.7)</td>
</tr>
<tr>
<td>Vitamin D, IU/100 calories</td>
<td>800-1000 IU/day</td>
<td>210 (126-453)</td>
<td>150 (90-270)</td>
</tr>
<tr>
<td>mOsm/kg H2O</td>
<td>450</td>
<td>326</td>
<td>450</td>
</tr>
</tbody>
</table>

(Amount in parenthesis is what is provided with goal feeds of 150 ml/kg/day. Compare to recommended levels)

*Assumes 1.6 g/100 calories

**Assumes 2.1 g/100 mL

***Assumes 2.1 g/100 mL

HMF=human milk fortifier.
## Calories and Protein Provided by LHMFs

<table>
<thead>
<tr>
<th></th>
<th>Human Milk, Mature/Term</th>
<th>Preterm Human Milk, &lt;29 weeks EGA</th>
<th>Donor Human Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories/ounce</td>
<td>19-21</td>
<td>20-26</td>
<td>15-20</td>
</tr>
<tr>
<td>LHMF 1, 4 vials + 100 mL</td>
<td>23-25</td>
<td>24-29</td>
<td>19-24</td>
</tr>
<tr>
<td>LHMF 2, 4 packets + 100 mL</td>
<td>23-25</td>
<td>24-29</td>
<td>19-24</td>
</tr>
<tr>
<td>LHMF 3, 20 mL + 100 mL</td>
<td>23-25</td>
<td>24-29</td>
<td>19-24</td>
</tr>
<tr>
<td>Protein, g/100 mL</td>
<td>0.9-1.5</td>
<td>2.2-3.3</td>
<td>0.8-1.4</td>
</tr>
<tr>
<td>LHMF 1, 4 vials + 100 mL</td>
<td>3.1-3.7</td>
<td>4.4-5.5</td>
<td>3-3.6</td>
</tr>
<tr>
<td>LHMF 2, 4 packets + 100 mL</td>
<td>2.9-3.5</td>
<td>4.2-5.3</td>
<td>2.8-3.4</td>
</tr>
<tr>
<td>LHMF 3, 20 mL + 100 mL</td>
<td>2.1-2.7</td>
<td>3.4</td>
<td>2-2.6</td>
</tr>
</tbody>
</table>

LHMF=liquid human milk fortifier.

Amy Gates, RD, CSP, LD and Jatinder Bhatia, 2016
Protein Intake, g/kg/d with fortification

Arslanoglu, Moro and Ziegler, J Perinatol 2009
Growth

- Premature infants fed fortified human milk experience better weight and length gain than those fed unfortified human milk
- No differences in long-term growth parameters
- However, infants fed fortified human milk [MOM or donor] receive less protein than assumed, grow slower

Schanler at al., 1999; Kuschel, Harding 2004; Schanler and Abrams 1995; Lucas et al., 1996; Miller et al., 2012; Arslanoglu et al., 2009; Bier et al., 2002; Carlson and Ziegler 1998., 2010
Calcium and Phosphorus

• Content in human milk is insufficient to achieve intrauterine accretion rates or normal bone mineralization
• Additional calcium and phosphorus is recommended after enteral feeds are established
• Impossible to meet requirements on parenteral nutrition
Calcium and Phosphate in Human Milk

Recommended enteral calcium requirement: 25-40 mmol/kg/d
Growth

- Better nutrient retention, increased bone mineralization
- Use of fortified milk approaches the net nutrient intrauterine rates of accretion
- Prevents a decrease in linear growth

Review: Multicomponent fortified human milk for promoting growth in preterm infants
Comparison: 1 Multicomponent fortification vs control (all trials)
Outcome: 13 Whole body bone mineral content (g)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment N</th>
<th>Treatment Mean(SD)</th>
<th>Control N</th>
<th>Control Mean(SD)</th>
<th>Mean Difference IV,Fixed,95% CI</th>
<th>Weight</th>
<th>Mean Difference IV,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faerk 2000</td>
<td>36</td>
<td>46.6 (9.9)</td>
<td>40</td>
<td>45.7 (8.2)</td>
<td>0.90 [-3.21, 5.01]</td>
<td>64.3 %</td>
<td>0.90 [-3.21, 5.01]</td>
</tr>
<tr>
<td>Wauben 1998</td>
<td>12</td>
<td>58 (6)</td>
<td>13</td>
<td>55 (8)</td>
<td>3.00 [-2.52, 8.52]</td>
<td>35.7 %</td>
<td>3.00 [-2.52, 8.52]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>48</td>
<td>48</td>
<td>53</td>
<td></td>
<td>100.0 %</td>
<td>1.65 [-1.65, 4.95]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0.0%
Test for overall effect: Z = 0.98 (P = 0.33)
Test for subgroup differences: Not applicable

Greer, McCormick 1988; Schanler, Abrams 1995; Schanler, Garza, Smith 1985; Horsman et al., 1989; Schanler, Garza 1988; Abrams et al., 1989
Figure 3. Forest plot of comparison: Fortified breast milk versus unfortified breast milk, outcome: 1.1 Weight gain (g/kg/d).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fortified</th>
<th>Unfortified</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>1.1.1 All trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modanlou 1986</td>
<td>26.7</td>
<td>3.4</td>
<td>8</td>
</tr>
<tr>
<td>Gross 1987 (1)</td>
<td>19.9</td>
<td>2.5</td>
<td>10</td>
</tr>
<tr>
<td>Gross 1987 (2)</td>
<td>21.6</td>
<td>3.5</td>
<td>17</td>
</tr>
<tr>
<td>Polberger 1989</td>
<td>20.4</td>
<td>2.8</td>
<td>7</td>
</tr>
<tr>
<td>Petrifor 1989</td>
<td>16.7</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>Porcelli 1992</td>
<td>11.4</td>
<td>2.7</td>
<td>10</td>
</tr>
<tr>
<td>Lucas 1996</td>
<td>15.6</td>
<td>4.7</td>
<td>137</td>
</tr>
<tr>
<td>Wauben 1998</td>
<td>16.6</td>
<td>1.6</td>
<td>12</td>
</tr>
<tr>
<td>Nicholl 1999</td>
<td>15.1</td>
<td>3.3</td>
<td>13</td>
</tr>
<tr>
<td>Mukhopadhyay 2007</td>
<td>15.1</td>
<td>4</td>
<td>82</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>310</td>
<td></td>
<td>99.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 32.63, df = 9 (P = 0.0002); I² = 72%
Test for overall effect: Z = 6.12 (P < 0.00001)

1.1.2 Trials recruiting only very preterm or VLBW infants

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fortified</th>
<th>Unfortified</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Modanlou 1986</td>
<td>26.7</td>
<td>3.4</td>
<td>8</td>
</tr>
<tr>
<td>Petrifor 1989</td>
<td>16.7</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>Polberger 1989</td>
<td>20.4</td>
<td>2.8</td>
<td>7</td>
</tr>
<tr>
<td>Nicholl 1999</td>
<td>15.1</td>
<td>3.3</td>
<td>13</td>
</tr>
<tr>
<td>Mukhopadhyay 2007</td>
<td>15.1</td>
<td>4</td>
<td>82</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>139</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 16.02, df = 4 (P = 0.003); I² = 75%
Test for overall effect: Z = 5.58 (P < 0.00001)

1.1.3 Trials conducted in low- or middle-income countries

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fortified</th>
<th>Unfortified</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Petrifor 1989</td>
<td>16.7</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>Mukhopadhyay 2007</td>
<td>15.1</td>
<td>4</td>
<td>82</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>111</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.94, df = 1 (P = 0.16); I² = 48%
Test for overall effect: Z = 3.15 (P = 0.002)

Test for subgroup differences: Chi² = 3.04, df = 2 (P = 0.22), I² = 34.2%
Figure 4. Forest plot of comparison: 1 Fortified breast milk versus unfortified breast milk, outcome: 1.2 Length gain (cm/wk).

1.2.1 All trials
- Modaniou 1986
  - Fortified: Mean = 0.99, SD = 0.4, Total = 8
  - Unfortified: Mean = 0.81, SD = 0.44, Total = 10
  - Weight = 1.6%
  - Mean Difference: IV, Fixed, 95% CI: 0.18 [-0.21, 0.57], Year: 1986

- Gross 1987 (1)
  - Fortified: Mean = 0.99, SD = 0.19, Total = 10
  - Unfortified: Mean = 0.81, SD = 0.22, Total = 10
  - Weight = 7.3%
  - Mean Difference: IV, Fixed, 95% CI: 0.08 [-0.10, 0.28], Year: 1987

- Gross 1987 (2)
  - Fortified: Mean = 0.84, SD = 0.25, Total = 17
  - Unfortified: Mean = 0.79, SD = 0.12, Total = 10
  - Weight = 11.8%
  - Mean Difference: IV, Fixed, 95% CI: 0.05 [-0.09, 0.19], Year: 1987

- Polberger 1989
  - Fortified: Mean = 1.2, SD = 0.17, Total = 7
  - Unfortified: Mean = 0.83, SD = 0.17, Total = 7
  - Weight = 7.5%
  - Mean Difference: IV, Fixed, 95% CI: 0.37 [0.19, 0.55], Year: 1989

- Porcelli 1992
  - Fortified: Mean = 0.6, SD = 0.2, Total = 10
  - Unfortified: Mean = 0.7, SD = 0.3, Total = 10
  - Weight = 4.8%
  - Mean Difference: IV, Fixed, 95% CI: -0.10 [-0.32, 0.12], Year: 1992

- Lucas 1996
  - Fortified: Mean = 0.93, SD = 0.47, Total = 137
  - Unfortified: Mean = 0.96, SD = 0.47, Total = 138
  - Weight = 19.3%
  - Mean Difference: IV, Fixed, 95% CI: -0.03 [-0.14, 0.08], Year: 1996

- Wauben 1998
  - Fortified: Mean = 1.1, SD = 0.2, Total = 12
  - Unfortified: Mean = 0.9, SD = 0.2, Total = 13
  - Weight = 9.7%
  - Mean Difference: IV, Fixed, 95% CI: 0.20 [0.04, 0.36], Year: 1998

- Mukhopadhyay 2007
  - Fortified: Mean = 1.04, SD = 0.3, Total = 82
  - Unfortified: Mean = 0.86, SD = 0.2, Total = 75
  - Weight = 38.0%
  - Mean Difference: IV, Fixed, 95% CI: 0.18 [0.10, 0.26], Year: 2007

Subtotal (95% CI) 283 (272) 100.0% 0.12 [0.07, 0.17]

Heterogeneity: Chi² = 22.71, df = 7 (P = 0.002), I² = 69%
Test for overall effect: Z = 4.80 (P < 0.00001)

1.2.2 Trials recruiting only very preterm or VLBW infants
- Modaniou 1986
  - Fortified: Mean = 0.99, SD = 0.4, Total = 8
  - Unfortified: Mean = 0.81, SD = 0.44, Total = 10
  - Weight = 3.3%
  - Mean Difference: IV, Fixed, 95% CI: 0.18 [-0.21, 0.57], Year: 1986

- Polberger 1989
  - Fortified: Mean = 1.2, SD = 0.17, Total = 7
  - Unfortified: Mean = 0.83, SD = 0.17, Total = 7
  - Weight = 15.9%
  - Mean Difference: IV, Fixed, 95% CI: 0.37 [0.19, 0.55], Year: 1989

- Mukhopadhyay 2007
  - Fortified: Mean = 1.04, SD = 0.3, Total = 82
  - Unfortified: Mean = 0.86, SD = 0.2, Total = 75
  - Weight = 80.7%
  - Mean Difference: IV, Fixed, 95% CI: 0.18 [0.10, 0.26], Year: 2007

Subtotal (95% CI) 97 (92) 100.0% 0.21 [0.14, 0.28]

Heterogeneity: Chi² = 3.67, df = 2 (P = 0.16), I² = 46%
Test for overall effect: Z = 5.80 (P < 0.00001)

1.2.3 Trials conducted in low- or middle-income countries
- Mukhopadhyay 2007
  - Fortified: Mean = 1.04, SD = 0.3, Total = 82
  - Unfortified: Mean = 0.86, SD = 0.2, Total = 75
  - Weight = 100.0%
  - Mean Difference: IV, Fixed, 95% CI: 0.18 [0.10, 0.26], Year: 2007

Subtotal (95% CI) 82 (75) 100.0% 0.18 [0.10, 0.26]

Heterogeneity: Not applicable
Test for overall effect: Z = 4.46 (P < 0.00001)

Test for subgroup differences: Chi² = 4.72, df = 2 (P = 0.09), I² = 57.6%
Figure 5. Forest plot of comparison: Fortified breast milk versus unfortified breast milk, outcome: Head growth (cm/wk).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fortified Mean</th>
<th>SD</th>
<th>Total</th>
<th>Unfortified Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3.1 All trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modanlou 1986</td>
<td>1.09</td>
<td>0.07</td>
<td>8</td>
<td>0.92</td>
<td>0.24</td>
<td>10</td>
<td>6.2%</td>
<td>0.27 [0.11, 0.43] 1986</td>
<td></td>
</tr>
<tr>
<td>Gross 1987 (1)</td>
<td>0.92</td>
<td>0.09</td>
<td>10</td>
<td>0.83</td>
<td>0.16</td>
<td>10</td>
<td>11.7%</td>
<td>0.14 [-0.02, 0.20] 1987</td>
<td></td>
</tr>
<tr>
<td>Gross 1987 (2)</td>
<td>0.84</td>
<td>0.21</td>
<td>17</td>
<td>0.84</td>
<td>0.09</td>
<td>9</td>
<td>11.3%</td>
<td>0.08 [-0.12, 0.21] 1987</td>
<td></td>
</tr>
<tr>
<td>Polberger 1989</td>
<td>1.11</td>
<td>0.13</td>
<td>7</td>
<td>0.94</td>
<td>0.25</td>
<td>7</td>
<td>3.5%</td>
<td>0.17 [-0.04, 0.38] 1989</td>
<td></td>
</tr>
<tr>
<td>Porcelli 1992</td>
<td>0.7</td>
<td>0.3</td>
<td>10</td>
<td>0.7</td>
<td>0.2</td>
<td>10</td>
<td>10.0%</td>
<td>0.10 [-0.22, 0.22] 1992</td>
<td></td>
</tr>
<tr>
<td>Lucas 1996</td>
<td>1.01</td>
<td>0.47</td>
<td>137</td>
<td>0.91</td>
<td>0.35</td>
<td>138</td>
<td>15.7%</td>
<td>0.08 [-0.04, 0.16] 1996</td>
<td></td>
</tr>
<tr>
<td>Wauben 1998</td>
<td>1.0</td>
<td>0.1</td>
<td>12</td>
<td>1.0</td>
<td>0.2</td>
<td>13</td>
<td>10.1%</td>
<td>0.10 [0.02, 0.22] 1998</td>
<td></td>
</tr>
<tr>
<td>Mukhopadhyay 2007</td>
<td>0.83</td>
<td>0.2</td>
<td>82</td>
<td>0.75</td>
<td>0.2</td>
<td>75</td>
<td>38.6%</td>
<td>0.08 [0.02, 0.14] 2007</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>283</td>
<td></td>
<td>272</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.08 [0.04, 0.12]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 8.96, df = 7 (P = 0.26), I² = 22%
Test for overall effect: Z = 4.21 (P < 0.0001)

1.3.2 Trials recruiting only very preterm or VLBW infants
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fortified Mean</th>
<th>SD</th>
<th>Total</th>
<th>Unfortified Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modanlou 1986</td>
<td>1.09</td>
<td>0.07</td>
<td>8</td>
<td>0.92</td>
<td>0.24</td>
<td>10</td>
<td>12.9%</td>
<td>0.27 [0.11, 0.43] 1986</td>
<td></td>
</tr>
<tr>
<td>Polberger 1989</td>
<td>1.11</td>
<td>0.13</td>
<td>7</td>
<td>0.94</td>
<td>0.25</td>
<td>7</td>
<td>7.2%</td>
<td>0.17 [-0.04, 0.38] 1989</td>
<td></td>
</tr>
<tr>
<td>Mukhopadhyay 2007</td>
<td>0.83</td>
<td>0.2</td>
<td>82</td>
<td>0.75</td>
<td>0.2</td>
<td>75</td>
<td>80.0%</td>
<td>0.08 [0.02, 0.14] 2007</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>97</td>
<td></td>
<td>92</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.11 [0.05, 0.17]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 5.22, df = 2 (P = 0.07), I² = 62%
Test for overall effect: Z = 3.88 (P = 0.0001)

1.3.3 Trials conducted in low- or middle-income countries
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fortified Mean</th>
<th>SD</th>
<th>Total</th>
<th>Unfortified Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mukhopadhyay 2007</td>
<td>0.83</td>
<td>0.2</td>
<td>82</td>
<td>0.75</td>
<td>0.2</td>
<td>75</td>
<td>100.0%</td>
<td>0.08 [0.02, 0.14] 2007</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>82</td>
<td></td>
<td>75</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.08 [0.02, 0.14]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 2.50 (P = 0.01)

Test for subgroup differences: Chi² = 0.74, df = 2 (P = 0.69), I² = 0%
## Multi-nutrient fortification of Human Milk

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Risk with fortified breast milk</th>
<th>Relative effect</th>
<th>N</th>
<th>Quality of Evidence [GRADE]</th>
</tr>
</thead>
<tbody>
<tr>
<td>g/kg/d</td>
<td>1.81 g/kg/d more [1.23-2.4]</td>
<td>-</td>
<td>635</td>
<td>Low</td>
</tr>
<tr>
<td>L, cm/wk</td>
<td>0.12 cm/wk, [0.07-0.17]</td>
<td>-</td>
<td>555</td>
<td>Low</td>
</tr>
<tr>
<td>HC, cm/wk</td>
<td>0.08 cm/wk, [0.04-0.12]</td>
<td>-</td>
<td>555</td>
<td>Moderate</td>
</tr>
<tr>
<td>MDI @ 18 m</td>
<td>2.2 [-3.35- +7.75]</td>
<td>-</td>
<td>245</td>
<td>Moderate</td>
</tr>
<tr>
<td>PDI @ 18 m</td>
<td>2.4 [-1.9- +6.7]</td>
<td>-</td>
<td>245</td>
<td>Moderate</td>
</tr>
<tr>
<td>NEC</td>
<td>40/1000 [19-82]</td>
<td>RR 1.57 [0.76-3.23]</td>
<td>882</td>
<td>Low</td>
</tr>
</tbody>
</table>

Brown et al, Cochrane Database of systematic reviews, DOI:10.1002/14651858.CD000343.pub3, 2016
Individualized Fortification and Fortifiers

Fig. 1. Preterm human milk (HM) protein (g) achieved with four different fortifier strategies* when fed at 150 mL and compared to estimated goals. Low P □; Expected P □; Expected P □; High P □. *Fortifier strategies: PTF: Preterm formula (Similac Special Care 30®, Abbott Nutrition, Columbus, OH); AC-LF: Acidified liquid fortifier (Mead Johnson Nutritionals, Evansville, IN); HMF +4: Prolacta Bioscience (Monrovia, CA); Powder: Enfamil Human Milk Fortifier (Mead Johnson Nutritionals, Evansville, IN).
Protein, Carbohydrate, fat and energy after target fortification

<table>
<thead>
<tr>
<th></th>
<th>ESPGHAN</th>
<th>BM</th>
<th>FIXED + BM</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, g/dL</td>
<td>2.7-3.0</td>
<td>1.2 ± 0.3</td>
<td>2.3 ± 0.3</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>Carb, g/dL</td>
<td>7.7-8.8</td>
<td>7.3 ± 1.1</td>
<td>7.7 ± 1.1</td>
<td>8.6 ± 1.2</td>
</tr>
<tr>
<td>Fat, g/dL</td>
<td>3.2-4.4</td>
<td>3.7 ± 0.8</td>
<td>4.7 ± 0.8</td>
<td>4.8 ± 0.8</td>
</tr>
<tr>
<td>Energy, kcal/dL</td>
<td>73-90</td>
<td>67 ± 9</td>
<td>82 ± 9</td>
<td>89 ± 8</td>
</tr>
</tbody>
</table>

Day-to-day variations in macronutrient intake would differ if breast milk is not analyzed daily.

*76/210 milk batches with fixed fortification required extra fortification with fat. Minimum 2 days a week need to be analyzed.*

adapted from Rochow et al., Nutrients 2015, 7:2297-2310
Human Milk Cream vs Standard Fortification

- Prospective, noninferiority, randomized, unblinded study
- 750-1250g, n=78
- Control group: mother’s own milk or donor HM fortified with human milk fortifier
- Cream group: as above + cream if HM < 20 kcal/oz
- Cream supplement is 25% lipids, 2.5 kcal/mL
- Assumption that HM was 20 kcal/oz
# Human Milk Cream

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Cream</th>
</tr>
</thead>
<tbody>
<tr>
<td>g/kg/d</td>
<td>12.4 [3.9]*</td>
<td>14.0 [2.5]</td>
</tr>
<tr>
<td>L, cm/week</td>
<td>0.83 [0.41]*</td>
<td>1.03 [0.33]</td>
</tr>
<tr>
<td>RTBW g/kg/d</td>
<td>13.7 [4.0]*</td>
<td>15.7 [2.5]</td>
</tr>
</tbody>
</table>
Exclusive Human Milk Fortification

- Preterm infants <37 weeks gestation [27.6 ± 2.0]
- BW <1250g [913 ± 182]
- Exclusive human milk-based diet
- Achievement of full feeds by 4 weeks of age
- Mother’s own milk supplemented with pasteurized donor milk [HMBA]
- Fortification began at 60 mL/kg/d [HMF60] with an additional 4 kcal/30 mL
- Additional 6kcal/30 mL at 100-120 mL/kg/d
- If weight gain less than 15g/kg/d within a week, 8kcal/30 mL fortification
- Assumed HM to be 0.67kcal/g, 0.9g/dL protein

Hair et al., bmcresnotes.biomedcentral.com/articles/10.1186/1756-0500-6-459, 2013
Human Milk Cream and Exclusive Human Milk-Based Diet

Hair et al., J Pediatr 2014;165:915-920
Exclusive Human Milk Fortification

* Sullivan et al; J Pediatr 2010
Exclusive Human Milk Fortification

• A more rapid fortification strategy [n=104]
• Exact intakes assumed as MOM + donor milk + fortifier was given
• SGA at birth 21%
• SGA at DC 43%
Protein Recommendations vs Estimated Intake: Donor and MOM

Protein intake estimation based on manufacturer’s estimations
Energy Recommendations vs Estimated Intake

150 ml/kg/day

28 weeks  32 weeks  37 weeks  40 weeks

- Recommendation
- MOM +LHMF 24
- MOM + LHMF 22
-- 1.0 to -1.99 At risk
-2 to -2.99 Moderate
<-3 Severe
Increased enteral protein intake in human milk-fed preterm infants

- <32 weeks gestation
- <1500g
- Enteral intake of at least 100 mL/kg/d by day 7
- Randomized 2:1:1
  - Lower protein [standard fortification, 5g/100 mL, FM85, Nestle]
  - Higher-protein
    - Higher protein supplementation using an investigational multicomponent fortifier
    - Individually adjusted fortification on top of standard fortification

Maas C et al., JAMA Pediatr 2017:171(1)16-22
Methods [continued]

• Lower protein: overall supply 3.5g/kg/d, assuming 1.3 g/100 mL in HM and fed at 150 mL/kg/d

• Higher protein aimed at 4.5g/kg/d

• Investigational fortifier: 1.8g bovine protein/5g fortifier [10.01.DE.INF; Nestle Nutrition]

• All three groups had fixed dose fortification of 2.5g/100 mL [100-149 mL/kg/d] and 5g/100 mL [150 mL/kg/d and thereafter]

• Group 2b: bovine protein added according to weight as well as MCT
Results

P: birth to end of intervention; P1: randomization to day 28
Results II

Energy Intakes

E, kcal/kg/d

Low Protein

High Protein

E1, kcal/kg/d
Plots for data points in time are separated only to enhance clarity of data presentation. Each data point represents the median value; error bars, interquartile range. Study interventions were continued for a median (interquartile range) of 41 (30-57) days and until definite discharge planning.
Weight gain velocity of preterm infants with the reference fetus and infant

Gestational age (weeks)

Reference
24 week
27 week
30 week

Reference

24 week

27 week

30 week

0 2 4 6 8 10
12 14 16 18 20
22 24 26 28 30 32 34 36 38 40 42 44 46 48

g/kg/day

Gestation age (weeks)
Summary of Fortification

• Adjustable fortification using BUN and growth appears to be a safe and suitable strategy
• When milk analyzers are made available [US], target fortification may be practiced
• Bedside analyzers currently in use over estimate human milk protein content by ~17% [Ziegler 2014]
• Day to day variation in human milk composition makes target fortification a labor intensive task
• More attention needs to be paid when using donor human milk
Feeding Premature and LBW Infants

- Balance the risk of under and over feeding particularly LBW infants who are small for gestational age
- Global epidemic of metabolic syndrome especially in countries where growth restriction rates are high
- For premature infants
  - Early aggressive parenteral nutrition
  - Early trophic feeds, colostrum swabbing
  - Human milk feeds with appropriate fortification
  - Monitor weight, length, head circumference

- Accepted goal is to achieve postnatal growth similar to that of a normal fetus
• Monitor growth
• Follow Up
• Premature infant
  • Early parenteral nutrition

Reduce time to regain birth weight

Colostrum
  • Mother’s own milk
  • Donor milk
  • Fortification

Neurocognitive advantage

Reduced infections, necrotizing enterocolitis

• Transition to enteral nutrition
• Monitor growth

Bhatia 2013
Summary

- Nutrition in premature and LBW infants is a continuum from birth through discharge and after
- Particular attention is needed during parenteral nutrition, human milk feedings
- Growth restriction still a problem: Nutrition or predisposition?
- Fortification strategies need to be improved
- Vitamin D and Iron supplementation
- Current recommendations need to be followed as most of the deficiency states are preventable
- ONE SIZE DOES NOT FIT ALL!!

Jatinder Bhatia, 2016
39th Annual
Neonatology: The Sick Newborn
Including NAS, PICC Line, and Pediatric Neonatal Vascular Ultrasound Courses

September 15 - 17, 2017

Presented by
Medical College of Georgia at Augusta University
Division of Professional and Community Education

Kiawah Island, South Carolina