Individual fortification of human milk

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Infants 22-25 weeks at NICU Lund, Sweden

Survival rate 2010: 82%

Year

Number

Survivors

Dead
Nutrition of preterm infants < 32 weeks

1. Mother’s own breast milk + fortification if needed
2. Donor breast milk (if available, preterm milk + fortification if needed)
3. (Preterm infant formula, to be avoided in infants < 34 weeks)
4. Supplementary parenteral nutrition
Enteral feeding

There is a long tradition in Sweden to start enteral feeding of all preterm infants with donor breast milk during the first 2-4 hours of life.
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Almost all mothers of preterm infants start pumping and maintain milk production during the preterm period (tube-feeding until 35-36 weeks of gestation).
Breast milk superiority over infant formula

Growing body of evidence supporting the use of HM for all neonates, including preterm infants

AAP, Pediatrics 2005;115:496

- Neurology – cognition
- Bioavailability
- Infections
- Retinopathy ROP
- Necrotizing enterocolitis NEC
- Gastrointestinal tolerance
Huge variation in human milk composition

Between women

During the course of lactation

From day to day and pumping to pumping

During the individual milk expression (increasing fat)

Depending on the pumping technique
Huge variation in human milk composition

- Hibberd, *Arch Dis Child* 1982;57:658
- Michaelsen, *JPGN* 1990;11:229
- Polberger, *JPGN* 1999;29:332
- Kent, *Pediatrics* 2006;117:e387
After evaluation of the various chemical methods of determining milk content of macronutrients, the infrared (IR) technique is used in most neonatal units in Sweden since the 90’s.

Lönnerdal B, Smith C, Keen CL.  

Polberger S, Lönnerdal B.  
*J Pediatr Gastroenterol Nutr* 1993;17:283
Human milk macronutrient analyses

- MID IR (Infrared)
- Protein (Kjeldahl)
- Lipids (Röse-Gottlieb)
- Carbohydrates, lactose (Luff-Schorl)
- Energy (calculation)
Human milk infrared (IR) analyses

- High precision and accuracy
- Low cost
- Immediate results

- Mother’s own milk: Always 24-hour collections, **not** spot samples once (twice) a week
- Donor milk at pasteurization
- Well-shaken samples
Volume breast milk per day 4L

Lactation day

mL
Protein, daily 24-hour-collections 4L

![Graph showing protein levels over lactation days]
Energy, daily 24-hour-collections 4l

[Graph showing energy consumption over lactation days with data points ranging from 50 to 110 kcal/dL]
Energy, daily 24-hour-collections 4L

Lactation day

kcal/dL
Energy, meal-to-meal-variation day 15-19 41

kcal/dL vs. Hours

0 24 48 72 96 120

Hourly energy consumption variations over a 120-hour period.
Volume in every milk collection day 15-19 4L

Volume measured in mL over time in hours.
<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Ingredients</th>
</tr>
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<tbody>
<tr>
<td>1919</td>
<td>Ylppö</td>
<td>1 % fat</td>
</tr>
<tr>
<td>1948</td>
<td>Jorpes</td>
<td>casein hydrolysate</td>
</tr>
<tr>
<td>1949</td>
<td>Hess</td>
<td>defatted bovine milk</td>
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<tr>
<td>1980</td>
<td>Lucas</td>
<td>&quot;a human milk formula&quot;</td>
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<td>1982-</td>
<td>Hagelberg</td>
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<td></td>
<td>Schanler etc</td>
<td></td>
</tr>
<tr>
<td>1985-</td>
<td>Tönz</td>
<td>bovine products</td>
</tr>
<tr>
<td></td>
<td>Modanlou etc</td>
<td></td>
</tr>
</tbody>
</table>
Lactoengineering

Lucas presented in 1980 “a human milk formula” which was the beginning of what is called lactoengineering

*Lucas A, Early Hum Dev 1980;4:15*
Fortification of human milk

What evidence do we have of fortification of HM?

Not very much. Cochrane review 2004:3:
10 RCT’s, > 600 infants with BW < 1850 g:

Fortification of HM compared with the feeding of unfortified HM was associated with small but statistically significant short-term improvements in weight gain (+2.33 g/kg/d), linear growth (+0.12 cm/week) and head circumference (+0.12 cm/week). These results support the use of HM fortification as a common practice in infants with BW < 1500, possibly < 2000 g to obtain optimal growth.
Fortification of HM – long-term effects

Only two studies have evaluated long-term growth effects of HM fortification – with no differences in weight, length or head circumference at 12 and 18 months of corrected age.

Lucas, Am J Clin Nutr 1996;64:142
Wauben, Acta Paediatr 1998;87:780
Fortification of HM – long-term effects

Only one study assessed developmental performance at 18 months of age – with test scores being higher but non-significant in the fortified group (Bailey MDI, PDI, social maturity).

These data are difficult to interpret because study infants in both groups received > 50% of their diet as preterm infant formula.

*Lucas, Am J Clin Nutr 1996;64:142*
HOW to fortify human milk?

The optimal method of HM fortification still remains to be determined, and a great number of protocols are being used throughout the world.

The most common approach is using a commercially available bovine multi-component packaged powdered fortifier – with varying compositions.

It is likely that the ideal fortifier would originate from HM, but it is not easily available – and has so far mainly been used for research purposes (exception is the Prolacta preparation in the US).
WHEN to start fortifying?

We can see very differing routines. From start at a few days of life until several weeks when enteral volumes of feeding can not be further increased.
Fortification of HM - multicomponent

- Protein
- Energy (lipids, carbohydrates)
- Minerals
- Trace elements
- Vitamins
Energy in HM fortifiers

The source is usually carbohydrates. But there are also fortifiers containing fat – with lower osmolality and improved gastrointestinal tolerance?

But there are formula studies indicating improved growth and protein synthesis with carbohydrates, compared with fat

(Kashyap, Pediatr Res 2001;50:390)
Energy and minerals

There are NO studies comparing fat or carbohydrates as the energy source in the HM fortifier

Minerals – different calcium salts may affect the lipid absorption in the GI tract
It can be questioned what clinical effect the osmolality of the HM fortifier has, but there are probably reasons to avoid > 400 mOsm/kg. (A low osmolality may improve the feeding tolerance)

Lucas, Am J Clin Nutr 1996;64:142
Berseth, Pediatrics 2004;114:699
Reis, Pediatrics 2000; 106:581
Individualized feeding methods

- Blind ("full strength" to all) – to be avoided
- Semiquantititative (mother’s own or donor milk?) – better
- **Individualized**
  
  Nutrient intakes – HM analyses IR (protein, energy)
  
  Metabolic response (serum urea, transthyretin, amino acids?)
Advantages of individualized fortification

Less risks of over- or undernutrition (CNS-toxicity), hyperosmolality
Advantages of individualized fortification

You can usually supply less amounts of fortifier – with less risk of CNS-toxicity and feeding intolerance (lower osmolality), less problems with GE reflux (Doege, Clin Nutr 2007;26:581)?

There are no studies on long-term effects of individualized fortification. But several short-term studies suggest improved growth.
Individualized fortification of HM

HM analyses (targeted fortification)

Polberger, JPGN 1993;17:283, 1999;29:332
Carvaglia, Arch Dis Child Fetal Neonatal Ed 2008;93:F372
De Halleux, Arch Pediatr 2007;14:S5
Aceti, JPGN 2009;49:613
Individualized fortification of HM

**Protein markers** (adjustable fortification), usually s-urea or BUN

- Georgieff, JPGN 1987;6:775
- Moro, JPGN 1995;20:162
- Cooke, J Perinatol 2006;26:591
- Arslanoglu J Perinatol 2006;26:614
- Cooke, J Perinat Med 2010;38:233
Protein markers

Reference values for growing, healthy preterm infants corresponding to 30 to 40 gestational weeks:

- Serum urea: 1-3 mmol/L
- Serum transthyretin: 90-140 mg/L

(data from Polberger et al.)
Nutritional status

- Growth
  - Weight
  - Length
  - Head circumference

- Milk analyses
  - Protein
  - Energy

- Protein markers
  - Serum urea
  - Serum transthyretin

- Clinical condition
Problems with fortification of HM

The intakes will usually become less than calculated. Particularly if the macronutrient content of HM has not been analyzed but assumed.

Carlson, J Perinatol 1998;18:252
Arslanoglu, J Perinatol 2009;29:489
Henriksen, Br J Nutr 2009;102:1179
Fortification of HM

Future?

Development from a single multi-component fortifier from each manufacturer (first-second generation fortifier) to various specific mono-component fortifiers, e.g. protein, energy (carbohydrates / fat), minerals etc?

Corvaglia, Early Hum Dev 2010;86:237
Fortification with HM products

New references

Czank, Breastfeed Med 2010;5:59

Sullivan, J Pediatr 2010;156:562 (lower risk of NEC with a HM fortifier compared to a bovine fortifier)
Fortification with HM products

Ideal situation?

The infants’s own mother’s milk – if in excess – is defatted and ultrafiltrated, and the components are used for fortification of her own milk.
Whay can be done?

- Use mother’s own milk as much as possible and minimize the use of donor HM (which often originates from mothers of full-term infants with lower protein content). Heat treatment of banked HM will result in lower fat absorption etc. Encourage the mothers to start early pumping (< 6 hours after birth, pumping frequency 8-12 times per day, stay with the baby at the hospital, kangaroo mother care etc.)

  
  Bishara, J Hum Lact 2009;25:272

- If donor HM is fortified – try to obtain as much HM as possible from mothers delivering preterm infants (with higher nutrient concentrations, preterm milk).
Individualized feeding in preterm infants Lund

- All donor milk is analyzed for macronutrient content
- The most protein-rich donor milk is given to a newborn preterm infant < 28 gestational weeks
- First analysis of own milk is performed after 10-14 dagar, then once a week
- Consider not only volumes but also what food is used, e.g. own milk, donor mature milk or infant formula
Individualized feeding in preterm infants Lund

- The milk is given in chronological order (in the order it has been pumped) to reduce the variation in nutrient content.
- The milk from 24-hour collections is mixed before administered or frozen – to reduce the meal-to-meal variation.
Individualized feeding in preterm infants Lund

- Calculate protein, energy and volume intakes
- Evaluate need for fortification including protein markers (serum urea, transthyretin)
- Start fortification if necessary, usually at the time when the volumes can not be further increased
- Fortifiers used are of bovine origin, but HM preparations would be preferable
- Target protein intake 3.5 - 4.5 g/kg/day and energy intake 110-135 kcal/kg/day (more if BPD)

*ESPGHAN, JPGN 2010;50:1-9*
Calculator for nutritional status

For immediate information on intakes of

- Protein (g/kg/day)
- Energy (kcal/kg/day)
- Glucose (mg/kg/min)
- Volume (ml/kg/day)
Breast is best