Nouvelles données sur les fortifiants du lait maternel

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Postnatal growth & further development in preterm infants

Weight gain during hospitalization

- cognitive development (2 years)
  *Ehrenkranz et al. 2006*

- renal function (8 years)
  *Bacchetta et al. 2009*

FFM accretion during hospitalization

- associated with improved speed of processing in preterm infants.
  *Pfister et al. 2013*

- associated with Improved neurodevelopment at 1 year CA for VLBW Infants.
  *Ramel J Pediatr 2016*

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Martin 2009: 23-27 weeks. Only those with a weight gain D7-D28 of **20-30 g/kg/j** had a z-score similar to z-score at birth.
# Fortification of HM

## Objectives:
To add precise amounts of fortifier without bacteriological contamination (hygiene)

## Standard fortification
**Multicomponent fortifier**

## Individualized fortification
**Multicomponent fortifier ± Protein, Fat, Carbohydrates**

<table>
<thead>
<tr>
<th></th>
<th>Milk preparation center</th>
<th>Dedicated room in or close to the unit</th>
<th>At bedside</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximity babies</strong></td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Hygiene</strong></td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Precision</strong></td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

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# Standardized fortification

Composition of multicomponent fortifiers and protein fortifier (per g powder)

<table>
<thead>
<tr>
<th>Name</th>
<th>Suppletine</th>
<th>Fortipré</th>
<th>Fortema</th>
<th>FM85</th>
<th>Enfamil</th>
<th>Similac</th>
<th>Nutriprem (Aptamil PS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Lactalis</td>
<td>Nestle</td>
<td>Danone</td>
<td>Nestle</td>
<td>MJ</td>
<td>Ross</td>
<td>Danone</td>
</tr>
<tr>
<td>Energy (Kcal)</td>
<td>3,6</td>
<td>3,5</td>
<td>3,5</td>
<td>3.6</td>
<td>4.9 (L)</td>
<td>3.9 (L)</td>
<td>3.4</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>0,2</td>
<td>0,2(^{PH})</td>
<td>0,3(^{PH})</td>
<td>0,2(^{EH})</td>
<td>0,4</td>
<td>0,3</td>
<td>0,8(^{PH})</td>
</tr>
<tr>
<td>Na (mg)</td>
<td>6,6</td>
<td>5.2</td>
<td>8,0</td>
<td>5.4</td>
<td>5.6</td>
<td>4.2</td>
<td>7.8</td>
</tr>
<tr>
<td>K (mg)</td>
<td>3,0</td>
<td>13.2</td>
<td>5,3</td>
<td>2.3</td>
<td>10.2</td>
<td>17.5</td>
<td>12.3</td>
</tr>
<tr>
<td>Ca (mg)</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>10</td>
<td>32</td>
<td>33</td>
<td>5.2</td>
</tr>
<tr>
<td>Ph (mg)</td>
<td>6</td>
<td>9</td>
<td>9</td>
<td>7</td>
<td>18</td>
<td>19</td>
<td>5.2</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>0</td>
<td>0,3</td>
<td>0</td>
<td>0</td>
<td>0,5</td>
<td>0,1</td>
<td>0</td>
</tr>
</tbody>
</table>

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Standardized fortification

May be inappropriate for some preterm infants fed HM:

✓ Slower growth than infants fed a preterm formula
✓ Significant proportion are growth retarded at discharge

Henriksen 2009: 127 VLBW infants fed fortified (std) HM
BW < P10: 33% at birth  ➔  58% at discharge

Due to

✓ Variability of nutrients needs in various clinical situations
  (ELBW, severe intrauterine growth restriction, BPD, …)

NB: ESPGHAN 2010
« No specific recommendations are provided for infants with a weight
below 1000 g because data are lacking …”
« The needs of infants with specific diseases (e.g., bronchopulmonary
dysplasia, congenital heart disease, short bowel syndrome) … are not
specifically addressed in this commentary.”

✓ Variability of nutrients’ content of human milk
Standardized fortification

Multicomponent fortifiers increase osmolality of HM

- Human milk $\approx 290-300$ mOsmol/kg

- No evidence was found for a causal relation between the osmolality of nutrients and the development of necrotizing enterocolitis.

- Delay in gastric emptying if osmolality $> 450$ mOsmol/kg

- Warning about feeding oral high osmolar electrolyte supplements and medications (Pearson 2012, Kriessl 2013)
Standard fortification of HM: 3 multicomponent fortifiers

**Protein intake (for 160 ml/kg/d) & osmolality (mOsm/kg)** *

- Increased risk > 450 mosm/kg

**Osmolality of new products!**

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Experimental study showed that adding fortifier and extra-hydrolysed proteins to preterm infant mothers’ milk increased osmolality

Rosas Acta Pediatr 2016

Fresh HM

Fortified with extensively hydrolyzed MCF (FM85)

± Protein supplement

¬ Osmolality up to 550 mosm/kg
What happens in the first 2 hours after fortification?

2/3 of the increase occurs immediately at time of fortification

Fortification « at bedside » is not efficient to prevent the significant increase in osmolality

Improve multicomponent fortifiers’ composition
Standardized fortification may help, but could be insufficient to cover the needs of preterm infants.

- **Improve standard fortification**
  - Early beginning,
  - Lipids as energy source,
  - Protein content

- **Individualized fortification**
  - Standardize HM composition
  - Targeted Fortification
  - Evaluate individual protein utilization
  - Adjustable Fortification

**Optimization of postnatal growth**
Standardized fortification may help, but could be insufficient to cover the needs of preterm infants.

**Improve standard fortification**
- Early beginning,
- Lipids as energy source,
- Protein content, ….

**Individualized fortification**
- Standardize HM composition
- Targeted Fortification
- Evaluate individual protein utilization
- Adjustable Fortification

**Optimization of postnatal growth**

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Early beginning of multicomponent fortification

Early versus Delayed Human Milk Fortification in Very Low Birth Weight Infants–A Randomized Controlled Trial (Shah 2016)

100 VLBW infants, multicomponent fortifier started at 20 or 100 ml/kg.d

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (g)</td>
<td>990</td>
<td>990</td>
</tr>
<tr>
<td>GA (wks)</td>
<td>27.5</td>
<td>28</td>
</tr>
<tr>
<td>SGA (&lt;P10) (%)</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Start to feed (d)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Age full feed (d)</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Feeding intolerance (%)</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Cumulative protein intake M1 (g/kg)</td>
<td>99</td>
<td>90</td>
</tr>
<tr>
<td>SGA at discharge (&lt;P10) (%)</td>
<td>72</td>
<td>68</td>
</tr>
</tbody>
</table>

No significant difference

➡ Higher protein intake (energy idem) but no significant effect on feeding tolerance or time to reach full feeding volume.

NB: 2/3 infants presented EUGR!
Standardized fortification
Improvement of fortifiers’ composition

*Human milk based fortifier*

- Not yet fully available in Europe (5 centers in Austria)
- Expensive
- HM consuming
- Ethical concern (paid donors)

- Efficacy reported only in NICUs with high prevalence of NEC (16%) (Sullivan et al. 2010)

Figure 2. NEC and NEC surgery in study infants. There were significant differences in NEC among the 3 groups (P = .05), *P = .04 vs BOV, **P = .09 vs BOV, ***P = .02 vs BOV. There were significant differences in NEC requiring surgical intervention among the 3 groups (P = .02), †P = .03 vs BOV, ‡P = .007 vs BOV. [ ] refers to number of infants.

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Standardized fortification
Improvement of fortifiers’ composition

* Lipids to replace partly carbohydrates as energy source *

➔ Multicenter randomized controlled trial: DIAMOND study

Control HM fortifier (cHMF=FM85) vs. New HM fortifier (nHMF):
Main outcome: weight gain over a 21 days-period

Secondary outcomes: digestive tolerance, LC-PUFA status, …..

<table>
<thead>
<tr>
<th>Control: HM + control HM fortifier (cHMF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental: HM + new HM fortifier (nHMF)</td>
</tr>
</tbody>
</table>

- ½ to full strength fortification
- Full strength fortification and full enteral feeds (150 – 180 mL/kg/day)
- Continue per MD

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# Composition of fortifiers

<table>
<thead>
<tr>
<th></th>
<th>Control HMF (cHMF) 5g/100mL</th>
<th>New HMF (nHMF) 4g/100mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>17.37</td>
<td>17.44</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>0.02</td>
<td>0.70</td>
</tr>
<tr>
<td>MCT (g)</td>
<td>0.0</td>
<td>0.6</td>
</tr>
<tr>
<td>DHA (mg)</td>
<td>0.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>3.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Maltodextrin (g)</td>
<td>3.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Lactose (g)</td>
<td>0.3</td>
<td>0.0</td>
</tr>
</tbody>
</table>
# Nutrients’ intake and osmolality

<table>
<thead>
<tr>
<th></th>
<th>cHMF</th>
<th>nHMF p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td><strong>Energy intake (kcal/kg.d)</strong></td>
<td>125</td>
<td>126 &gt; 0.05</td>
</tr>
<tr>
<td><strong>Protein intake (g/kg.d)</strong></td>
<td>3.8</td>
<td>4.5 &lt; 0.05</td>
</tr>
<tr>
<td><strong>Osmolality at H24 (mosm/kg)</strong></td>
<td>425  / 475</td>
<td></td>
</tr>
</tbody>
</table>

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## EFFICACY

### Weight gain

<table>
<thead>
<tr>
<th></th>
<th>cHMF</th>
<th>nHMF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>74</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Weight gain (g/kg.d)</td>
<td>16</td>
<td>17</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

### LC-PUFAs

<table>
<thead>
<tr>
<th>DHA at D21</th>
<th>cHMF</th>
<th>nHMF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell phosphatidylethanolamine</td>
<td>5.1</td>
<td>5.6</td>
<td>0.016</td>
</tr>
</tbody>
</table>

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TOLERANCE

• Digestive tolerance
  No difference

• Metabolic tolerance: Serum urea

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In summary, the new fortifier

Increased protein content (en protein to energy ratio) helped to improved short-term weight gain

Replacement of carbohydrates by lipids $\Rightarrow$ reduction of osmolality $\Rightarrow$ good digestive tolerance

Improvement of LC-PUFAs status
Standardized fortification may help, but could be insufficient to cover the needs of preterm infants.

Improve standard fortification

Individualized fortification

- Standardize HM composition
- Evaluate individual protein utilization

Targeted Fortification

Adjustable Fortification

Optimization of postnatal growth

Lipids as energy source, protein content, early beginning

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Individualized fortification of HM

Targeted Fortification
Analysis of HM and then fortification to reach the targeted nutrient intake (NB: requires frequent milk analyse) by adding:

- **protein**: Polberger 1999
- **lipids**: De Halleux 2007
- **prot, fat, carbohydrates**: Rochow 2013, McLeod 2016 RCT Marlocchi 2016

→ Makes an assumption about nutrient’s needs
  (ESPGHAN 2010: HM! ELBW!)

Adjustable fortification
Protein fortification adjusted to the metabolic response evaluated through periodic determinations of serum urea

- Arsanoglu 2010 RCT
- Alan 2015

→ Takes into consideration actual protein status in each infant

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Individualized targeted fortification of HM

Rochow 2013: single center, prospective case-control study

<table>
<thead>
<tr>
<th>HM + HMF (Similac)</th>
<th>Only ±Fat±Prot±Carbohydr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=10)</td>
<td>(n=20)</td>
</tr>
<tr>
<td>BW (g)</td>
<td>880±240</td>
</tr>
<tr>
<td>GA (wks)</td>
<td>27.1±1.6</td>
</tr>
<tr>
<td>ΔP (g/kg/d)</td>
<td>19.7±3.3</td>
</tr>
</tbody>
</table>

⇒ Weight gain similar in both groups (< fetal growth rate!)

McLeod 2016. N=20/group: VLBW (<30 weeks), AGA

Fortification based on assumed composition to target 3.8-4.4 g protein/kg.d & 130-150 kcal/kg.d.

⇒ Weight gain similar in both groups (< fetal growth rate!)
⇒ No difference in anthropometry and fat mass % at discharge

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Adjustable protein fortification in VLBW infants

N=32 VLBW (≈31 weeks, 1400g) [RCT] (Arsanoglu 2006)
HM+ std fortification bovine HMF (FM85) until ≈ D18
Then adjustable protein fortification ProMix (whey protein) according to blood urea level

- <3 mMol/L (9 mg/dL): +1 level of fortification
- > 5 mMol/L (14 mg/dL): -1 level of fortification
- 3 - 5 mMol/L (9-14 mg/dL): no change

Based on bovine HMF (FM85) ± ProMix (whey prot: 0.3g/0.4g per g powder)

**Main outcome criteria:**
Weight gain

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>STD</th>
<th>ADJ</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (g/day)</td>
<td>24.8±4.8</td>
<td>30.1±5.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(g/kg/day)</td>
<td>14.4±2.7</td>
<td>17.5±3.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Length gain (mm/day)</td>
<td>1.1±0.4</td>
<td>1.3±0.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Head circumference gain (mm/dy)</td>
<td>1.0±0.3</td>
<td>1.4±0.3</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean ± s.d.

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In summary, (pragmatic) fortification of HM

- **Start**
  ✓ Early: well-tolerated enteral intake at 50 to 80 ml/kg.d
  ✓ Multicomponent fortification (well-tolerated & efficient)

- **Increase** of fortified HM intake up to well-tolerated full-ental feeding (160-180 ml/kg.d)

- **Monitor**
  ✓ Tolerance (digestive & metabolic)
  ✓ Weight gain

- **Individualize** fortification (monitor carefully postnatal growth)
  ✓ **Targeted**? If dedicated staff and infrared analyzer(s)
  ✓ **Adjustable**? Easier (no assessment of HM composition) and proven short-term efficacy on weight and HC growth

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CONCLUSION

Available products allow individualized nutrition that could help to optimize the nutritional care of preterm infants fed human milk.

Strategy of HM fortification should be decided based on evidence and feasibility (staff, organization) in each unit and based on a common policy unit.

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You are welcome!

In Lyon, France
July 7-9, 2017
International Neonatal Association
(70 countries)

In Glasgow, UK
October 5-6, 2017
European Milk Bank Association
(210 HM banks)

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