Early-life programming effects on long-term productivity of dairy calves

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Developmental programming: The concept

Developmental programming involves a critical time window in early life.
Factors involved in developmental programming?
Maternal status

- Prenatal exposure to maternal metabolic stress
  (Ling et al., JDS 2018)
# Maternal nutrition and postnatal life

<table>
<thead>
<tr>
<th>Maternal Diet</th>
<th>Energy density</th>
<th>Rumen-protected methionine (RPM)</th>
<th>Organic trace minerals (ORG, Zn, Cu, Mn, and Co)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong> NEL = 5.25 MJ/kg of DM vs. <strong>High</strong> NEL = 6.48 MJ/kg of DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Body height</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>↓ Body length</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>↓ T lymphocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Total antioxidant capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Gao et al, JDS 2012)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Control vs. RPM**

<table>
<thead>
<tr>
<th>Maturation of hepatic gluconeogenesis</th>
<th>Growth rates</th>
<th>Wither height</th>
<th>Body weight</th>
<th>Hip height</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Jacometo et al, JDS 2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(Xu et al, JDS 2018)</td>
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</tbody>
</table>

**ORG vs. Sulfate sources**

<table>
<thead>
<tr>
<th>Oxidative stress Status Down-regulation of inflammatory mRNA and miRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Jacometo et al, JDS 2015)</td>
</tr>
</tbody>
</table>
Role of Nutrition

- **Lactocrine hypothesis**
  Bartol et al., 2008

  - Milk-borne bioactive factors (MbFs)
    - Immunoglobulin (Ig)
    - Bioactive peptide (Cytokines)
    - Lactoferrin
    - Hormones and growth factors, (IGF-I, EGF, TGF and relaxin)
    - Oligosaccharides
    - Immune-related miRNAs
Lactocrine hypothesis

Administration of colostrum / transition milk after gut closure

Replacement of vacuolated fetal-like intestinal epithelium by mature intestinal epithelium

Bittrich et al., 2004

Lactocrine programming window

Bittrich et al., 2004

Maximum efficacy of IgG absorption
Fischer et al., 2018

First 24 h

First 6 h

Gut closure

MBFs

Hours

0h  6h  12h  24h  48h

Birth

Time of life
Success of lactocrine signaling

↑ Neonatal immune system
  Fischer et al., 2018

↑ Gut development
  villus height, crypt depth,
  Cell proliferation and differentiation
  Baumrucker et al., 1994

↑ Colonization with beneficial bacteria
  Bifidobacterium and ↓ E. coli
  Malmuthuge et al., 2015

↓ Pathogens` adherence
  to the intestinal epithelial cells and prevent infections - Oligosaccharides
  Maldonado-Gomez et al., 2015

↑ Mucosal immune system
  in the small intestine
  Liang et al., 2014

↑ Milk production at first and second lactation
  Faber et al. 2005

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  villus height, crypt depth,
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Disruption of lactocrine signaling

- ↑ Impaired energy metabolism particularly glucose absorption, Hammon et al., 2012, 2013
- ↑ Failure of passive transfer linked with increased calf morbidity and mortality Donovan et al., 1998
- ↓ Slower bacterial colonization Malmuthuge et al., 2015
- ↓ Weaning weight and ADG Lago et al., 2017
- ↓ Long-term productivity Faber et al. 2005
- ↑ Culling rate during the first lactation Faber et al. 2005

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<table>
<thead>
<tr>
<th>Study (high vs. low milk)</th>
<th>Response (milk production)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foldager et al., 1997</td>
<td>+ 572 kg</td>
</tr>
<tr>
<td>Bar-Peled et al., 1997</td>
<td>+ 454 kg</td>
</tr>
<tr>
<td>Ballard et al., 2005</td>
<td>+ 242 kg</td>
</tr>
<tr>
<td>Shamay et al., 2005</td>
<td>+ 132 kg</td>
</tr>
<tr>
<td>Pollard et al., 2007</td>
<td>+ 836 kg</td>
</tr>
<tr>
<td>Aikman et al. 2007</td>
<td>---------------</td>
</tr>
<tr>
<td>Raeth-Knight, 2009</td>
<td>+ 718 kg</td>
</tr>
<tr>
<td>Terré et al., 2009</td>
<td>+ 624 kg</td>
</tr>
<tr>
<td>Morrison et al., 2009</td>
<td>− 91 kg</td>
</tr>
<tr>
<td>Davis-Rincker et al., 2011</td>
<td>+ 416 kg</td>
</tr>
<tr>
<td>Kiezebrink et al., 2015</td>
<td>− 25 kg</td>
</tr>
<tr>
<td>Korst et al. 2017</td>
<td>+ 612 to + 725 kg</td>
</tr>
</tbody>
</table>
Preweaning nutrient intake & mammary gland development

<table>
<thead>
<tr>
<th>Item</th>
<th>Control</th>
<th>Enhanced</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole mammary gland, g</td>
<td>75.48</td>
<td>337.58</td>
<td>29.14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mammary gland as % of BW</td>
<td>0.12</td>
<td>0.41</td>
<td>0.03</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mammary parenchyma, g</td>
<td>1.10</td>
<td>6.48</td>
<td>1.00</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mammary parenchyma as % of BW</td>
<td>0.002</td>
<td>0.008</td>
<td>0.001</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Adapted from Soberon and Van Amburgh, 2017 JDS
Fetal programming of muscle development

Nutrient restriction ↓ Muscle fiber and mass ↓ Muscle fiber hypertrophy, ↓ Birth weight, ↓ Adipogenesis, ↓ marbling in calf

Adapted from Du et al., 2010 J Anim Sci.
Developmental programming of gut

Critical Window of gut development

- Prenatal
- Birth
- First week
- First 2-3 months
- Adult animal

Milk borne bioactive factors (MBFs)

Tight-junction protein coding genes
Mucosal immune system
Initial gut microbial colonization
Liang et al., 2016, Malmuthuge and Guan, 2017

Fetal nutrient supply

Postnatal growth
- Continued growth (Rumen)
- Adaptation to diet changes (weaning)

Plane of nutrition
Maternal heat stress and its long term effects

- Immune development preweaning,
- Culling cattle before puberty,
- BW at weaning and puberty,
- Weight gain during preweaning

↓ Uterine blood flow, ↓ Placental weight

↓ IgG absorption from colostrum

↓ Birth weight, ↓ Immunity

↓ Fertility, ↓ Milk production,
↑ Number of services per conception
Take home messages

- Programming occurs in neonatal dairy calves and early life events have long-term effects on calf performance.

- Delivery of MBFs from cows to calves in early life plays a pivotal role in the programming of later life performance by affecting immune system maturation, and gut development.

- Fetal gestation is a critical window of skeletal muscle development in ruminant and maternal under-nutrition would compromise postnatal birth weight and growth.
Take home messages

- Preweaning plane of nutrition may altered programming of mammary gland development in dairy calves and can shift it to an allometric phase of growth.
- There are multiple developmental windows for the small intestine during perinatal, and neonatal periods in dairy calves and programming of this plastic tissue seems to play a critical role in later growth, health, and performance.

- Maternal heat stress or maternal under-nutrition may impact immune function and metabolism of dairy calves as well as future lactational performance.
Thank you for your attention
Types of epigenetic modifications