The transition period and metabolic diseases in relation to fertility

Stephen LeBlanc
## Transition Health and CR at 1\textsuperscript{st} AI

5719 cows in 7 US herds

Table 2. Impact of health problems in the first 60 d postpartum on pregnancy at first postpartum AI of dairy cows\(^1\)

<table>
<thead>
<tr>
<th>Health status</th>
<th>Prevalence</th>
<th>Pregnant, %</th>
<th>Adjusted OR (95% CI)(^2)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health problem</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>56</td>
<td>51.4</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1 case of disease</td>
<td>27</td>
<td>43.3</td>
<td>0.79 (0.69 – 0.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt; 1 case of disease</td>
<td>17</td>
<td>34.7</td>
<td>0.57 (0.48 – 0.69)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Type of health problem(^3)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calving problem</td>
<td>15</td>
<td>40.3</td>
<td>0.75 (0.63 – 0.88)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Metritis</td>
<td>16</td>
<td>37.8</td>
<td>0.66 (0.56 – 0.78)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Clinical endometritis</td>
<td>20</td>
<td>38.7</td>
<td>0.62 (0.52 – 0.74)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fever postpartum</td>
<td>21</td>
<td>39.8</td>
<td>0.60 (0.48 – 0.65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mastitis</td>
<td>12</td>
<td>39.4</td>
<td>0.84 (0.64 – 1.10)</td>
<td>0.20</td>
</tr>
<tr>
<td>Clinical ketosis</td>
<td>10</td>
<td>28.8</td>
<td>0.50 (0.36 – 0.68)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lameness</td>
<td>7</td>
<td>33.3</td>
<td>0.57 (0.41 – 0.78)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
<td>32.4</td>
<td>0.63 (0.32 – 1.27)</td>
<td>0.20</td>
</tr>
<tr>
<td>Digestive problem</td>
<td>2</td>
<td>36.7</td>
<td>0.78 (0.46 – 1.34)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Santos et al RepDomRum 2010
Dry period nutrition and reproduction

• Pooled analysis of 7 studies of controlled ($\leq$ 100% NRC) vs. high (> 100% NRC) energy factorial experiments in far-off and close-up dry period (Cardoso et al 2013)

• CE in close-up associated with
  – Shorter time to pregnancy (157 vs 167 d)
  – Higher $\text{NE}_L$ intake postpartum
Patterns of DMI in the transition period

Increased Haptoglobin Precedes Reproductive Disease

Hp ≥ 1 g/L at 3 DIM OR = 6.7 for metritis  Se = 50% Sp = 87%

Huzzey et al 2009

Hp > 0.8 g/L in week +1 increased odds of metritis, PVD, and endometritis (OR = 1.6 – 2.2) (Dubuc et al 2010)
Association of haptoglobin with DMI

Inflammation

- Acute/classical inflammation
  - Injury → heat, pain, swelling, redness
  - Infection → fever, decreased feed intake
  - Disease causes inflammation

- Metabolic/chronic inflammation
  - No clinical signs
  - Oxidative stress, obesity, fat mobilization (?) → Slight elevations in pro-inflammatory mediators and acute phase proteins; changes in signalling
    - Contributes to insulin resistance
  - Inflammation contributes to disease

Adapted from Barry Bradford
Associations of inflammation and metabolism

54 cows tested – lowest and highest 20% “Liver Functionality Index” (score based on albumin, cholesterol and bilirubin at 3 DIM and Δ 3 to 28 DIM (n=6 per group) presented

Hypocalcemia – moving the goal posts?

• Subclinical hypocalcemia traditionally defined as < 2.0 mmol/L 1 – 3 DIM

In week 1 postpartum (2365 cows in 55 herds Canada & US; Chapinal et al JDS 2011, 2012)

• Ca ≤ 2.2 mmol/L (38% of cows) OR = 2.7 for DA (accounting for NEFA week -1 and +1)

• Ca ≤ 2.1 mmol/L (23% of cows)
  • -2.6 kg at 1st DHI test
  • ~ 29 % vs. 35% CR at 1st AI
Association of blood calcium with neutrophil function

- 110 cows in 1 herd in Florida
- Pair-matched “high risk” (twins, stillbirth, dystocia, RP) with low risk cows
- Subclinical hypo-Ca = ≤ 2.15 mmol/L at least once 1 – 3 DIM
Effect of Ca supplements

33 multiparous Holstein x Jersey cows Fed negative DCAD close-up diet

2 Bovikalc 12 h apart

Blanc et al 2014
Prevention or treatment of hypocalcemia

• One study (Miller and Oetzel, 2012) supplemented cows with oral calcium after calving found:
  • an increase in milk production in higher producing cows
  • decrease in health problems among lame cows
• Calcium supplements can reduce clinical milk fever
• Calcium supplements can modestly increase blood [Ca] in cows with low blood [Ca] (Miltenburg et al, 2016; Blanc et al 2016; Martinez et al 2016; Amanlou et al 2016)
• Effects of calcium supplements on risk of disease
  • None Miltenburg et al, 2016
  • None to worse Martinez et al 2016 a, b
  • Better Amanlou et al 2016
Re-esterified triglyceride

Stored in liver

Completely oxidized \rightarrow energy

Incompletely oxidized \rightarrow ketones

BHB

Acetoacetate

Acetone

Successful response to NEB

~ 50%

Propionate AA

Gluconeogenesis

Glucose

Fetus

Mammary gland

LCFA in milk

Exported in VLDL

NEFA
Re-esterified triglyceride

Stored in liver

NEFA

Unsuccessful response to NEB – Ketosis and Fatty liver

Propionate AA

Gluconeogenesis

Gluconeogenesis

Completely oxidized \(\rightarrow\) energy

Incomplete oxidized \(\rightarrow\) ketones

Re-esterified \(\rightarrow\) triglyceride

BHB

Acetoacetate

Acetone

LCFA in milk

Mammary gland

Fetus

Exported in VLDL

Glucose

Incompletely oxidized \(\rightarrow\) ketones

Unsuccessful response to NEB – Ketosis and Fatty liver

LCFA in milk
Association of serum NEFA and DA

NEFA in week -1 and +1 are more predictive of disease than BHBA alone (Ospina et al 2010; Chapinal et al 2011) but can’t be measured cow-side or on-farm.

Data from Chapinal et al 2011
## Associations of NEFA with health and performance

<table>
<thead>
<tr>
<th>Week relative to Calving</th>
<th>Source</th>
<th>Cut-point mmol/L</th>
<th>Outcome</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>Chapinal 2011</td>
<td>0.3</td>
<td>Retained Placenta</td>
<td>OR = 1.8</td>
</tr>
<tr>
<td>-1</td>
<td>Quiroz-Rocha 2007</td>
<td>0.4</td>
<td>Retained Placenta</td>
<td>OR = 1.2</td>
</tr>
<tr>
<td>-1</td>
<td>Chapinal 2011</td>
<td>0.3</td>
<td>Metritis</td>
<td>OR = 1.8</td>
</tr>
<tr>
<td>-1</td>
<td>Chapinal 2011</td>
<td>0.5</td>
<td>Displaced Abomasum</td>
<td>OR = 2.4</td>
</tr>
<tr>
<td>-2 or -1</td>
<td>Ospina 2010</td>
<td>0.3</td>
<td>RP, Metritis or DA</td>
<td>RR = 1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>305 ME milk</td>
<td>-683 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pregnancy by VWP + 71 d</td>
<td>HR = 0.81</td>
</tr>
<tr>
<td>-1</td>
<td>LeBlanc, 2005</td>
<td>0.5</td>
<td>Displaced Abomasum</td>
<td>OR = 3.6</td>
</tr>
<tr>
<td>-1</td>
<td>Chapinal 2012</td>
<td>0.5</td>
<td>Milk Yield</td>
<td>↓ 1.6 kg/d</td>
</tr>
<tr>
<td>-1</td>
<td>Carson, 2008</td>
<td>0.3</td>
<td>1\textsuperscript{st} Test LS</td>
<td>↑ 0.24</td>
</tr>
<tr>
<td>+1</td>
<td>Chapinal 2011</td>
<td>1.0</td>
<td>DA</td>
<td>OR = 3.1</td>
</tr>
<tr>
<td>+1 or 2</td>
<td>Ospina 2010</td>
<td>0.6</td>
<td>RP, Metritis or DA</td>
<td>RR = 4.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.7</td>
<td>Pregnancy by VWP + 71 d</td>
<td>HR = 0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.7</td>
<td>305 ME milk</td>
<td>-647 kg</td>
</tr>
</tbody>
</table>
Association of serum BHBA and DA

Ketosis typically precedes DA
BHBA increase starts before calving but is most predictive in week +1

Data from Chapinal et al 2011
Impacts of ketosis
Health and production

Subclinical ketosis (serum BHB > 1.0 – 1.4 mmol/L) in early lactation is associated with:

• 4-8X increased risk of LDA
  Geishauser, 2000; LeBlanc et al, 2005; Ospina et al 2010a
• Decreased milk production (-1.2 to 3.3 kg/d) at test 1 > 1.2 in week 1 and 1.4 in week 2; yet increased full lactation yield when 1.0 to 1.6 mmol at week +2
  Duffield, 2009
• 1.8 X increased odds of culling < 60 DIM
  Roberts et al 2012
• Increased severity of mastitis
  Suriyasathaporn et al, 2000
• Inconsistent effects on neutrophil function
**Impacts of ketosis - Reproduction**

Subclinical ketosis (serum BHB > 1.0 – 1.4 mmol/L) in early lactation is associated with:

- 3 X Increased risk of metritis (not in all studies)  
  Hammon et al 2006; Duffield et al 2009

- 1.4 X greater odds of endometritis (uterine inflammation based on cytology) at 35 DIM  
  Dubuc et al 2011

- 1.5 X increased odds of being anovular (not cyclic) at 63 DIM (19% vs. 13% of cows)  
  Walsh et al 2007; Dubuc et al 2012

- Decrease in pregnancy at first AI  
  Walsh et al, 2007

- Point prevalence (20 cows, 1 test, BHB ≥ 1.4 mmol/L) ≥ 20% associated with herd annual pregnancy at 1st AI < 40%  
  Dubuc & Denis-Robichaud, 2017

- BHB > 1.2 mmol/L in any of 1st 5 weeks postpartum associated with lower 6-week in-calf in pasture system (78 vs. 85%)  
  Compton et al 2015
Impacts of ketosis
Reproduction

- Ketosis in week 1 or 2 decreased pregnancy rate (Walsh et al 2007)
  - Median time to pregnancy (days) CR at 1\textsuperscript{st} AI
    - 108 (no ketosis) 42%
    - 124 (ketosis in 1 week) 36%
    - 130 (ketosis for 2 weeks) 28%
    \[ P=.003 \]
Cow-side tests for ketosis
(relative to serum BHB ≥ 1.4 mmol/L)

**Milk**

**Keto-Test**
- 100 µmol/L
  - Sensitivity = 83%
  - Specificity = 82%
- 200 µmol/L
  - Sensitivity = 54%
  - Specificity = 94%
  - Oetzel, 2004
- Cost = $2/test
- Powder lacks sensitivity

**Urine**

**Ketostix**
- (read at 5 seconds)
  - “small” (15µmol/L)
    - Sensitivity = 79%
    - Specificity = 96%
  - Carrier et al, 2004
  - Cost = $0.25/test

**Blood**

**Precision XTRA (Freestyle Neo)**
- Sensitivity = 87-100%
- Specificity = 74-100%
- Iwersen, 2009; Bach 2016
- Cost = $2/test
- Alternatives: NovaVet; TaiDoc (Bach 2016)
  ± NovaMax (LeBlanc)

Systematic review and meta-analysis of diagnostic tests for ketosis: Tatone et al PVM 2016
# Ketosis is a global problem

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Diagnostic criteria</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA, Canada</td>
<td>2365 cows, 55 herds BHB ≥ 1.2 mmol/L</td>
<td>Week 1: 18% of cows Week 2: 19% of cows</td>
<td>Chapinal et al 2010</td>
</tr>
<tr>
<td>EU (UK, Netherlands, Italy, Germany, France)</td>
<td>4709 cows, 7-21 DIM, &gt; 12 cows/herd, 1 test/cow, 131 herds Milk BHB ≥ 100 µmol/L</td>
<td>39% of cows 85% of herds had &gt; 25% prevalence</td>
<td>Berge &amp; Vertenten 2014</td>
</tr>
<tr>
<td>Canada</td>
<td>20 cows/herd, 1-14 DIM 126 herds point prevalence BHB ≥ 1.4 mmol/L</td>
<td>Median herd prevalence= 19%</td>
<td>Dubuc &amp; Denis-Robichaud 2017</td>
</tr>
<tr>
<td>New Zealand</td>
<td>40 cows/herd1620 cows, 57 herds BHB ≥ 1.4 mmol/L</td>
<td>7-12 DIM: 17% of cows 14% mean herd prevalence</td>
<td>Compton et al 2014</td>
</tr>
<tr>
<td>New Zealand</td>
<td>Weekly testing 585 cows, 15 herds BHB ≥ 1.2 mmol/L</td>
<td>1st week prevalence: 18% Cumulative 5 week incidence: 67%</td>
<td>Compton et al 2015</td>
</tr>
</tbody>
</table>
Cumulative Incidence of Ketosis
Weekly testing of 1653 cows on 17 farms

Weekly point prevalence = 20%
2 week cumulative incidence
Average = 43%
Minimum = 15%

Gordon, 2013
Impact of ketosis on immune function

Suriyasathaporn et al. 2000

Economic cost of ketosis

- $289 US/case (McArt et al 2015)

- €257/case (95% prediction interval €72 – 442 (Raboisson et al 2015)
Routine ketosis screening and treatment

• Large study in New York & Wisconsin, 2010
  • All fresh cows tested 3X per week
  • ½ treated with propylene glycol, ½ untreated
• Treated cows had:
  • Shorter time to ketosis cure (~ 5 vs 7 d)
    • ↑ ketosis cure – 1.5x
    • ↑ milk production – 0.69 kg/d to 30 DIM (varied by herd)
    • ↓ DA risk – 0.63x
    • ↓ culling risk – 0.32x

McArt et al, 2011 and 2012
Glucose measurement to guide ketosis treatment

- 2 clinical trials
  - **2011** n = 687 cows (17 herds) with BHB ≥ 1.2 mmol/L
    - 3 d glycol ± 25 ml Catosal® SC/d x 3 d ± 200 IU insulin glargine (Lantis) SC once (Gordon et al JDS 2017a)
  - **2012** n = 594 cows (9 herds) with BHB ≥ 1.2 mmol/L
    - 3 or 5 d of glycol ± 25 ml Catosal® SC/d x 3 d (Gordon JDS 2017b)
  - Interactions of treatment with blood glucose at diagnosis in both
**Ketosis treatment summary**  
Gordon et al JDS 2017a,b

- Based on ketosis cure +1 and +2 weeks and milk yield to 30 DIM
- Blood BHB ≥ 1.2 but < 2.4 mmol/L (or KetoTest = 100)
  - **Treat with 3 d glycol 300g 1X/day**
- Blood BHB > 2.4 mmol/L (KetoTest ≥ 200)
  - **Treat with 5 d glycol**
- If BHB > 1.2 mmol/L and glucose < 2.2 mmol/L (38% of cases)
  - **Add treatment with Catosal or B12 (1.25 mg) for 3 d**
    - Re-test at end of treatment
- Addition of dexamethasone not recommended (Tatone et al 2016)
Testing and treatment programs (McArt et al 2014)

• Models of cost-benefit of treating every cow vs. testing 1 – 3 X/week; all ketotic cows treated with propylene glycol for 5 d

• Given the model assumptions and their variations, for herds with 15 to 50% incidence of ketosis, most cost-effective was to test 2X per week between 3 and 9 DIM (identified 80% of cases)

• Herd DA and early culling risk were the most influential variables (greater benefit at higher risks)
Ketosis prevention

• Only 11% of the variation in the incidence of ketosis was explained by cow-level risk factors (parity, BCS) (data from Duffield et al 1998)

• A large part of the controllable variation lies at herd or management level:
  • Bunk space and feed availability
  • Movement and grouping
  • Heat abatement
  • Feed quality
  • TMR consistency
  • Water access
  • Monensin capsule
Cows with post-partum metritis had lower DMI during the post- and pre-partum periods

Huzzey et al. 2007
During the week before calving cows that develop post-partum severe metritis (n=12) consume less feed during the period immediately following fresh feed delivery (F.D.).

![Graph showing feed intake by healthy, mildly metritic, and severely metritic cows.](https://via.placeholder.com/150)

Courtesy of Dr. M. von Keyserlingk

Huzzey et al. 2007
Space – not the final frontier

• Despite recommendations to provide <80% stocking, controlled studies have not found this to benefit health

• 80% vs. 100% cows: headlocks in Jerseys (Silva et al 2014; Lobeck-Lutherhand et al 2015)
  • Changes in behaviour but no effects on health

• 80% stocking + 45 cm feeding space vs. 120% cows: stalls + 90 cm feeding space for 3 wk prepartum (Miltenburg, 2015)
  • Increased feeding competitive behaviour but no overall effects on metabolic health or immune function

• Stable vs. dynamic social groups (Silva et al 2013)
  • No effects on metabolic health or immune function
Risk factors for uterine disease

- Species of bacteria
  - Virulence factors
  - Strain
- Level of contamination

- Dry matter intake
- Energy and lipid metabolic health
- Stressors & hormonal changes
- Hypocalcemia

Bacteria

Immune response
Regulation of inflammation
Reproductive tract infection and inflammation

Endometritis

Purulent Vaginal Discharge

Each affects 15 – 20% of cows
Concepts of inflammatory response

Uterine Inflammation

Healthy

Endometritis – excessive inflammation

Endometritis – inadequate response

1 2 3 4 5 weeks
Transition sets the stage for fertility

126 herds in Quebec, Canada

Dubuc & Denis-Robichaud JDS 2017

<table>
<thead>
<tr>
<th>Herd prevalence threshold (estimated from 20 cows)</th>
<th>Herd pregnancy at 1st AI &lt; 40%</th>
<th>Herd pregnancy loss &gt; 5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP</td>
<td>-</td>
<td>≥ 5%</td>
</tr>
<tr>
<td>Ketosis (tested only once 1-14 DIM)</td>
<td>≥ 12%</td>
<td>-</td>
</tr>
<tr>
<td>PVD</td>
<td>≥ 5%</td>
<td>≥ 5%</td>
</tr>
<tr>
<td>Endometritis (cytobrush)</td>
<td>≥ 19%</td>
<td>-</td>
</tr>
<tr>
<td>Anovular (blood P4 30-44 and 44-57 DIM)</td>
<td>≥ 21%</td>
<td>-</td>
</tr>
<tr>
<td>DA</td>
<td>≥ 4 %</td>
<td>-</td>
</tr>
</tbody>
</table>
## Transition checklist

**Goal:** Optimize metabolic health & immune function  
**Means:** Manage cows to maintain feed intake

### Management
- Feed daily for 3-5% left over; ideally $\geq 2X/d$
- $\geq 75$ cm feed bunk space per cow
- $\leq 85\%$ cows: freestalls
- $> 11$ m$^2$ of bedded pack/cow
- $> 5$ m$^2$ of shade/cow; $> 55$ m$^2$ of drylot
- Build for 130-140% of average monthly calvings
- Large enough stalls; adaptation
- $< 24$ h in calving pen
- Minimize group changes
- Separate heifers if it does not violate the above
- Heat abatement (fans, soakers) when THI $> 68$
- BCS $= 3.0 - 3.5$ at calving

### Transition diet
- 3-4 weeks on close-up diet or 6 weeks as 1 dry group
- Meet but do not exceed E requirement 8 to 3 weeks prepartum
- Water ad lib; 10 cm linear per cow; 2 sources per pen
- $\geq 1000$ IU vitamin E/d; up to 2000 IU/d for RP; 0.3 ppm selenium (Ideally $\sim 6$mg/d)
- DCAD $< -100$ mEq/kg; Urine pH $< 6.5$

### Monitoring
- NEFA $< 0.3-0.4$ in last week prepartum; $< 0.7-1.0$ in week 1
- BHB $< 0.8$ mM in week -1
- BHB $< 1.1$ mM in week 1
- BHB $< 1.2$ mM weeks 2 – 3
- Ca $> 2.15$ mmol/l in week 1