Health in the Transition Period and Reproductive Performance

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Take Home Messages

- Essentially all dairy cattle experience a period of insulin resistance, reduced feed intake, negative energy balance, hypocalcemia, reduced immune function, and bacterial contamination of the uterus soon before, or in the weeks after calving.
- Health through the dry period and early lactation is a major determinant of reproductive performance for months after.
- Retained placenta, metritis, and endometritis are strongly associated with immune function in the transition period.
- High non-esterified fatty acid (NEFA) (> 0.4 mmol/L) in the last 7 to 10 days before expected calving is associated with increased risk of displaced abomasum (DA), retained placenta, culling before 60 days in milk, and less milk production in the first 4 months of lactation.
- Subclinical ketosis (serum β-hydroxybutyrate (BHB) > 1200 to 1400 μmol/L) in the first or second week after calving is associated with increased risk of DA, metritis, clinical ketosis, endometritis, prolonged postpartum anovulation, increased severity of mastitis, and lower milk production in early lactation. There are several validated and practical tools for cow-side measurement of ketosis.

Metabolic Challenges in Peripartum Dairy Cows and Their Associations with Reproduction

This paper reviews the importance of energy metabolism in transition dairy cows, its associations with disease and reproduction, and strategies for monitoring cows under field conditions during this critical time.

The biology of dairy cow health and reproductive performance is multifactorial

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and complex. High producing dairy cows have been described as "metabolic athletes". However, 30 to 50% of dairy cows are affected by some form of metabolic or infectious disease around the time of calving. Dairy cattle have been selected to re-partition nutrients in support of milk production, a process in which homeostatic mechanisms are at least partially and temporarily overridden, including a period of physiologic insulin resistance. Essentially all peripartum dairy cattle experience: a period of insulin resistance, reduced feed intake, negative energy balance, lipolysis, and weight loss in early lactation; hypocalcemia in the days after calving; reduced immune function for 1 to 2 weeks before, and 2 to 3 weeks after calving; and, bacterial contamination of the uterus for 2 to 3 weeks after calving. These factors, as well as dramatic changes in circulating progesterone, estrogen, and cortisol concentrations contribute to a substantial reduction of immune function, in particular of neutrophils, at this time (Goff and Horst, 1997). Specifically, innate immunity from neutrophils is a primary means of immune response in the uterus and neutrophil migration and phagocytic and oxidative activity are associated with the risk of retained placenta (RP) (Kimura et al, 2002), metritis, and endometritis (Hammon et al, 2006). Yet, while metabolic and uterine disease are common, only a minority of cows experience these problems, between herds or even with a herd in which cows apparently have similar nutritional and management experiences. Prediction or early detection of which cows have health problems is an important goal.

Peripartum cattle do go through a period of substantial insulin resistance that has elements in common with Type 2 diabetes, with the important difference that cows have low blood glucose. Dairy cattle also go through a period of substantial fat mobilization. High circulating non-esterified fatty acid (NEFA) concentrations are a major risk factor for fatty liver and may also have direct effects on neutrophil function (Scalia et al, 2006). Because of both high metabolic demands and pathogen challenges, cattle also routinely experience substantial oxidative stress at the same time (Sordillo and Aitken, 2009).

To achieve the economic objective of pregnancy within 80 to 120 days after the previous calving, the uterus must return to a condition to support a new pregnancy, and a regular estrous cycle must be re-established. This is the result of a complex set of interactions and endocrine signalling among the brain, liver, ovaries and uterus (Wathes et al, 2007). While there is some research on the links between energy metabolism and reproductive function, there is a gap in examining the intervening component of uterine disease, which is at play in as many as half of all cows. Uterine health problems (RP, metritis (uterine infection causing systemic illness in early lactation), and endometritis (chronic low-grade uterine infection and inflammation between 3 and 9 weeks postpartum) affect up to half of all dairy cows in the first 60 days postpartum (Sheldon et al, 2006).

Retained placenta is a disease of immune function, with changes in immune function at least two weeks before calving (Kimura et al, 2002). Cows that had RP had substantially higher serum cortisol for several days before parturition (Peter and Bosu, 1987) which may be one contributor to impairment of neutrophil function. Similarly, endometritis is associated with impaired innate immune function (Sheldon et al, 2009; Herath et al, 2009), again with measurable changes present prepartum (Kim et al, 2005), weeks before disease becomes manifest. Cows in greater negative energy balance, and in particular those that go on to have metritis or endometritis have more pronounced impairment of at least some immune functions (Hammon et al, 2006). Cows in a greater degree of negative energy balance prepartum, as evidenced by higher NEFA concentrations were 80% more likely to have RP, and accounting for the effect of NEFA, those with lower circulating vitamin E were at greater risk of RP (LeBlanc et al, 2004). This supports the notion that severe negative energy balance impairs immune function, which in turn makes RP more likely, but also underlines the fact that the development of RP is multifactorial. Metabolic disease that becomes clinically manifest as displaced abomasum, typically around 10 days postpartum, is preceded by significant changes in adipose mobilization and energy metabolism up to 3 weeks before the disease event (LeBlanc et al, 2005). It is increasingly clear that uterine disease that is expressed 1 to 8 weeks after calving, and return to a normal estrous cycle and ovulation by 9 weeks after calving are preceded by metabolic and immunologic changes before and soon after calving. While metabolic and immune function can be studied in detail for research, there are indicators or surrogate measures that are practical for clinical use.

The mechanisms of immune defence in the udder, and how these are impaired in the transition period have been reviewed (Burvenich, 2007). However, little is known about the determinants of uterine health, and how resistance to uterine disease may be enhanced through animal management. Contamination of the uterus with potentially pathogenic bacteria is nearly universal after calving (Sheldon et al, 2004), yet only a minority of cows develop clinical disease. Similar to RP, development of metritis depends largely on immune function in the early postpartum period (Hammon et al, 2006). Cows with severe metritis ate 2 to 6 kg dry matter less than healthy cows in the 2 to 3 weeks preceding the clinical signs of metritis (Huzzey et al, 2007). Lower feed intake is associated with increased NEFA which contributes to the risk of fatty liver, which in turn is associated with impaired neutrophil function (Zerbe et al, 2000). Additionally, NEFA have been shown to inhibit neutrophil function *in vitro* (Scalia et al, 2006). Healthy cows clear the uterus of bacteria by approximately 3 weeks postpartum but important gaps remain in understanding of the immunobiology of the reproductive tract of cattle. Approximately 17% of cows fail to clear bacterial infection and have clinical endometritis (LeBlanc et al, 2002) and an additional 15 to 20% have chronic subclinical inflammation (Gilbert et al, 2005). Both forms of endometritis are associated with substantial decreases in pregnancy rate. Recent research (Santos et al, 2008) indicates that uterine infection predominated by *E. coli* in the first week postpartum and *A. pyogenes* in the third week is associated with subsequent endometritis.

In summary, metabolic events starting two weeks before calving have effects on reproductive health 1 to 9 weeks after calving, which in turn have effects on reproductive performance weeks to months later. The determinants of why some cows develop uterine health problems are not well understood, which limits the ability to intervene to prevent these problems or mitigate their effects.

▪ Monitoring Programs

Objectives - Routine, proactive actions, observations, or analysis are intended to accurately and efficiently provide early detection of problems, to provide an opportunity for investigation and intervention in order to limit the consequences and costs of health problems and reduced animal performance or welfare. There are two main reasons for monitoring transition dairy cows in general, and running metabolic tests in particular. The objectives overlap, but are distinct and should be clear before embarking on a program. The objectives are: herd or group level - to monitor the success of current management with the goal of early detection of problems or deviation from the management program; individual level – to identify cows at high risk for disease with the goal of intervention for these individuals to prevent or mitigate clinical disease.

Methods of Monitoring

The principles and practice of screening programs for fresh cows have been well and critically described (Guterbock, 2004).

Clinical Disease Records

A starting point for assessment of peripartum health is to have accurate records of the farm-specific incidence of the clinical diseases of importance to the herd. This would typically include the number of cattle that had dystocia, RP, milk fever, metritis, and DA, or that were culled or died in early lactation divided by the number of cows that calved in a defined time period. The incidence of clinical mastitis and lameness per month or other time period is also useful although complicated by the risk period extending throughout lactation and the possibility for multiple occurrences in the same cow, which may not be independent events. For all diseases, it is important that the case definitions be clear, mutually exclusive, and consistently recorded. The records should allow for measurement of the incidence of the condition of interest, not the treatment rate (e.g. if some cases of RP are not treated the disease event should still be recorded; conversely if a condition is treated for 3 days, there should only be 1 recorded occurrence of the disease (as opposed to 3 treatment events). Investigation of the pattern of affected animals and the risk factors for disease is suggested if the following crude lactational incidence risks are exceeded: dystocia > 20%; RP > 10%; milk fever > 2%; metritis > 10%; DA > 5%. However, herd size, demographics, and management influence the expected incidence, so reference to herd-specific goals and recent history are more useful than broad benchmarks. Also, tracking the rates of clinical disease is necessarily retrospective and therefore at best allows for reaction to problems rather than early warning. Finally, clinical disease is typically only the “tip of the iceberg” with respect to health problems and therefore these records underestimate the prevalence of potentially performance-limiting health conditions. Trends in the prevalence of culling in early lactation may also provide an additional element of herd-level information (Nordlund and Cook, 2004).

Measurement of Feed Intake

Adequate feed intake by all peripartum cattle is crucial for health and production. It is therefore desirable to measure feed dry matter intake (DMI) in prepartum and early postpartum cows. Although measurement of only group average intake may be feasible in commercial free-stall barns, that is still likely to be useful information. For example, if there is < 2% of feed remaining prior to the first feeding of the next day, then ad libitum intake is likely not being achieved by all animals in the group. Assessment of individual feed intake and lack of competition for feed access are advantages of tie-stall housing.

Milk Production

Milk production is expected to increase rapidly in early lactation, and a consistent rise should result from good health and feed intake. Therefore, automated daily measurement of milk production in the first few weeks of lactation offers promise as a means to identify cows with clinical or subclinical health problems. The variability of daily milk yield is high, especially in early lactation, and is influenced by many factors beyond health (e.g. weather, changes in diet, movement of cattle to new groups, etc). However, decreased milk production often precedes clinical disease, and daily yield coupled with activity monitoring may be useful for screening of cows for earlier disease detection (Edwards and Tozer, 2004). Trends in projected production from early lactation provide herd-level information on the success of transition into lactation (Nordlund and Cook, 2004).

Body Condition Scoring

Body condition scoring (BCS) provides a rapid, simple, and acceptably precise estimate of body fatness. It reflects the nutritional, metabolic, and to some extent, health history of a cow in the preceding weeks. Numerous studies have examined the association of BCS with health and reproduction (Bewley and Schutz, 2008), and while generally cows that calve in fat body condition, or moreover cows that lose 1 point or more of BCS in early lactation, are often reported to be at higher risk of adverse outcomes, BCS alone (other than extremes i.e. > 4 or < 2.5 at calving) is not a sensitive or specific tool for prediction of disease or reproductive performance. Recent research has suggested that the target BCS at calving should likely be lower (≤ 3.0) than previously advocated to optimize health and production (Garnsworthy, 2008).

■ Screening Cows for Uterine Disease

The pathophysiology (Sheldon, 2008), diagnostic criteria and treatment for metritis have been reviewed elsewhere (LeBlanc, 2008). Briefly, metritis may practically be identified based on fetid discharge, fever, and signs of systemic illness (dullness, inappetance, or decreased milk production). Cows with at least two of these signs are likely to benefit from 3 to 5 days of systemic treatment with ceftiofur or penicillin. Daily monitoring of rectal temperature for 7 to 10 days after calving may increase the rate of diagnosis of metritis, and if this practice is implemented it should not be the sole basis for treatment with antibiotics. Routine, systematic screening of fresh cows is likely useful to increase early detection of health problems, especially in large herds, but it is likely most useful if training and experience of personnel and facilities allow for assessment of the cows' attitude, appetite, ketosis status (once or twice weekly), rumination, and abomasal displacement.

Accurate diagnosis of clinical endometritis requires examination of discharge in the vagina after a minimum of 3 weeks postpartum (LeBlanc et al, 2002), which may be done with a vaginoscope, clean gloved hand, or a Metricheck device (Pleticha et al, 2009). Subclinical endometritis is common and has substantial impacts on reproductive performance (Gilbert et al, 2005). Subclinical endometritis is diagnosed by endometrial cytology obtained trans-cervically either by uterine lavage or cytobrush. Neither technique is sufficiently rapid or practical for widespread use in clinical practice.

Metabolites to Measure Energy Status in Transition Cows

Circulating concentrations of NEFA and β-hydroxybutyrate (BHB) measure aspects of the success of adaptation to negative energy balance. The concentration of NEFA reflects the magnitude of mobilization of fat from storage and mirrors DMI (Adewuyi et al, 2005), while BHB reflects the completeness of oxidization of fat in the liver. Ketone bodies (BHB, acetone and acetoacetate) are the intermediate metabolites of oxidation of fatty acids, specifically resulting from the incomplete oxidation of fatty acids. As the supply of NEFA to the liver exceeds the ability of liver to completely oxidize the fatty acids to supply energy, the amount of ketone production increases. Ketone bodies can be used by muscle as an alternative fuel source to glucose, sparing glucose for milk production. However, ketone production does not result in as much net energy release as complete oxidation of fatty acids. Additionally, increasing concentrations of ketones are thought to suppress feed intake (Allen et al, 2009).

Glucose is the primary metabolic fuel, and is absolutely required for vital organ function, fetal growth, and milk production. In dairy cows, the massive energy demand to support milk production is largely met through gluconeogenesis. Glucose concentrations are under tight homeostatic control. Therefore, although glucose has a central role in metabolism, it is a poor analyte for monitoring or investigating herd problems.

Associations of NEFA and BHB with Disease, Production, and Reproduction

High NEFA (> 0.4 mmol/L) in the last 7 to 10 days before expected calving is associated with: 2 to 4 times increased risk of left displaced abomasum (LDA; LeBlanc et al, 2005); 2 times increased risk of retained placenta (Quiroz-Rocha et al 2009); 2 times increased of culling before 60 days in milk (DIM) and 1.5 times increased risk of culling over the whole lactation (Duffield et al, 2005); and 1.1 kg/day less milk production in the first 4 months of lactation (Carson, 2008).

Subclinical ketosis (BHB > 1200 to 1400 μmol/L) in the first or second week after calving is associated with: 3 to 8 times increased risk of LDA (Duffield et al, 2009); 3 times greater risk of metritis when serum BHB in week 1 was > 1200 (Duffield et al, 2009); 4 to 6 times increased risk of clinical ketosis (Duffield et al, 2009); increased probability of subclinical endometritis at week 4 postpartum (Hammon et al, 2006); and increased duration and severity of mastitis but not with the incidence of mastitis (Duffield et al, 2009). Milk yield at first test was reduced by 1.9 kg/d when BHB was > 1400 μmol/L in week 1 and by 3.3 kg/d when BHB was > 2000 μmol/L in week 2. Cows with serum BHB > 1800 μmol/L in week 1 had > 300 kg lower projected production for the whole lactation.

Ketosis is associated with reduced reproductive performance, which extends its impact much longer than many producers realize. It is worth emphasizing that health in the weeks before and after calving influences reproduction at least 2 months later. Cows with milk BHB > 100 μmol/L in the first week postpartum were 1.5 times more likely to have not ovulated even by 9 weeks postpartum (Walsh et al, 2007a). Cows that experienced ketosis in the first two weeks of lactation had reduced probability of pregnancy at the first insemination (Figure 1).

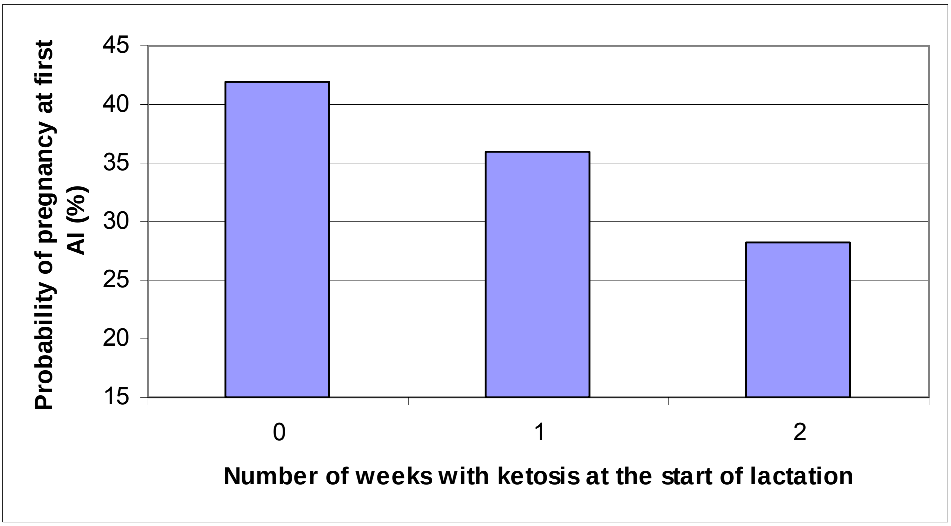

Figure 1. The association of the occurrence and duration of ketosis in early lactation with pregnancy at first insemination. Ketosis was defined as serum BHB > 1000 μmol/L in week 1 and > 1400 in week 2 postpartum. (Data from Walsh et al, 2007)

Furthermore, cows that had ketosis in one or both of the first two weeks after calving had a lower pregnancy rate until 140 DIM. The median interval to pregnancy was approximately 108 days in cows without ketosis, was significantly longer (124 days) in cows with ketosis in the first or second week postpartum, and tended to be longer still (130 days) in cows that had subclinical ketosis in both of the first weeks of lactation (Walsh et al, 2007).

Testing Strategies and Interpretation

Serum or plasma NEFA concentrations measured 4 to 10 days before expected calving provide a uniquely useful component of assessment of peripartum health. Unfortunately, there are presently no on-farm diagnostic tests for measurement of NEFA, which implies the cost and delay of submission of samples to a diagnostic laboratory. The concentration of NEFA typically begins to rise 2 to 4 days before, and peaks approximately 3 days after calving, but the magnitude of increase is greater, and the increase starts earlier in cows that subsequently experience metabolic disease (LeBlanc et al 2005).

Numerous studies in Canada indicate that the vast majority of subclinical ketosis occurs within the first two weeks postpartum, with few new cases thereafter. Such ketosis is associated with management in the pre-fresh, maternity, and early post-fresh periods. A comprehensive investigation including disease and culling records and overall assessment of nutritional and management practices, and the distribution of the time postpartum at which subclinical ketosis occurs may give direction to further investigation and a working diagnosis. When ketosis is detected primarily in the first two weeks postpartum, emphasis should be placed on bringing cows to the dry period in moderate body condition (BCS = 3 to 3.5), avoidance of excess energy intake between dry-off and 3 weeks prepartum (Drackley, 2007) and particularly on measures to enhance feed intake in the last few weeks before, and through the calving period. Further investigation of an elevated prevalence of ketosis in early lactation may be aided by NEFA testing of cows in the 10 days before expected calving. If there is little evidence of ketosis in the first two weeks postpartum, but an increased incidence 3 to 6 weeks postpartum, that suggests that preventive measures should emphasize enhancing feed intake in the post-fresh period.

Used with knowledge of their test characteristics to inform interpretation, serum BHB, whole blood BHB measured with Precision XTRA®, milk BHB measured with Keto-Test®, or Ketostix® in urine are valid diagnostic tests for subclinical ketosis. These 3 cow-side tests are economical, practical and sufficiently accurate relative to laboratory analysis of serum for use in the field (Oetzel, 2004).

Investigation of Underlying Causes, and Intervention

Several practical guidance documents for investigation of health problems in transition dairy cows by veterinary practitioners or other advisors have been put forward (Mulligan et al 2006; O'Boyle, 2008; Cook and Nordlund, 2004; Nordlund et al, 2006; Nordlund, 2008). The critical principles are to investigate and ensure that all cattle have unrestricted access to feed at the time of fresh feed delivery, to clean water, and to a comfortable resting place (Table 1).

Table 1. Suggested partial checklist of parameters to monitor or investigate health in peripartum dairy cows

Goal: *Optimize energy metabolism and immune function to favour uterine health and reproductive performance*
Means: *Manage cows to provide feed and resting access to maintain intake in the transition period*
Management • Feed for 2 to 5% left over TMR • ≥ 75 cm (30”) bunk space per cow, or 4 cows per 5 headlocks • ≤ 85% stocking density (cows to free stalls) or > 100 sq. ft of bedded pack/cow • Build to have stall and feeding capacity for 140% of the average monthly number of calvings • Separate heifers from cows if possible • Minimize the number of group and diet changes • < 24 h in individual calving pens • Heat abatement when THI (temperature humidity index)> 72 (> 26°C) • BCS = 3.25 - 3.5 at calving
Nutrition • 3-4 weeks on close-up diet or 5-6 weeks as 1 dry group • Feed to provide but not exceed maintenance requirements between 8 to 6 and 3 weeks before calving (i.e. from dry-off to close-up) • Fresh feed daily • Water ad lib; 2 sources per pen; 10 cm of trough space per cow
Monitoring • NEFA < 0.4 mEq/L in last week prepartum; < 1.0 in week 1 postpartum • BHB < 1100 μmol/L in week 1; < 1400 μmol/L in weeks 2 – 4 after calving

Unfortunately, there is presently little evidence to inform choices of intervention in individual cows in response to elevated NEFA or BHB. Administration of propylene glycol, insulin, or corticosteroids might be beneficial, but further research is needed on treatment regimes that might be effective at reducing the risk of disease or reduced performance among cows identified at high risk of these problems. Based on currently available data (Nielsen and Ingvartsen, 2004), propylene glycol may be a reasonable treatment for cows with elevated NEFA or BHB.

■ Conclusions

The timing, magnitude, and duration of peripartum increases in circulating concentrations of NEFA and BHB are associated with the risk of abomasal displacement, uterine disease, and reproductive performance from 1 through 20 weeks later. Programs to monitor management of the transition period may usefully include NEFA concentrations in the week before expected calving and BHB concentration in the first week after calving. A key link among diseases is feed intake. Peripartum energy metabolism and immune function will plausibly be favoured when cows have unrestricted access to diets formulated to meet nutrient requirements and to water in the transition period. Proactive management and investigation of problems should focus on minimizing nutritional, housing, social, and environmental factors that may impair feed and resting access for all or some members of the groups of peripartum cows.

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