Transition Period Health and Reproduction: Preparing for a Successful Pregnancy

Stephen LeBlanc

Population Medicine, University of Guelph, Ontario, Canada N1G 2W1
sleblanc@uoguelph.ca

▪ Take-Home Messages

- If both clinical and subclinical conditions are comprehensively monitored, 30 to 50% of cows experience at least one disorder in the transition period, most of which are associated with impaired reproductive performance. However, healthy cows, even at high production, have good fertility.
- Avoidance of reproductive disease and loss of more than 0.5 point of body condition score are important for reproductive performance.
- Effective monitoring and treatment programs for metritis and purulent vaginal discharge can limit the consequences of these problems.

▪ Introduction

Clinical diseases in dairy cows such as retained placenta and metritis are obvious, but subclinical disease may have greater effects on herd reproductive performance because the incidence may be greater and cases may go untreated. There is an opportunity for farmers and their advisors to assess ketosis, hypocalcemia, and subclinical reproductive disease (purulent vaginal discharge and endometritis) and put monitoring and treatment programs in place. These problems may be associated with impaired fertility for two to six months after occurrence. Ongoing management to prevent metabolic health problems supports productivity and reproduction.

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. A glucose deficit, hypocalcemia, mobilization of body fat, ketosis, and systemic inflammation influence immune response in transition cows and all these change rapidly and vary substantially between cows.

Links between postpartum disease and fertility are well established. The consequences of difficult calving, milk fever, and displaced abomasum are immediate and obvious. However, other less obvious problems may have greater effects on herd reproductive performance because they affect greater proportions of cows and may go undetected and untreated.

A dataset on nearly 6000 cows from seven large, high-production herds in the U.S. illustrates the prevalence and health disorders in the transition period and their associated consequences for reproduction (Santos et al., 2010). Unsurprisingly, each of dystocia, metritis, endometritis, ketosis, and lameness was associated with reduced probability of pregnancy at first insemination. The sobering statistic was that, when disease was comprehensively monitored, only 56% of cows got through the transition period without at least one clinical or subclinical condition. On the other hand, healthy cows had excellent fertility, with 51% pregnant at first service, and had fewer pregnancy losses than did cows that experienced health problems, notwithstanding high production (average 305 d milk yield was ~ 11,000 kg). Additional studies using large datasets form single herds confirmed these associations and underlined the additive negative effects of having more than one clinical disease on pregnancy rates (Carvalho et al., 2019; Pascottini et al., 2020).

These incidence rates are expected considering both clinical diseases (i.e., visible, obvious conditions such as retained placenta) and subclinical conditions for which routine examination or testing is required, such as ketosis and purulent vaginal discharge (PVD). For example, weekly or semi-weekly screening for ketosis in the first two weeks postpartum reveals that on average, 40% of cows experience ketosis (McArt et al., 2012; Gordon et al., 2017). When examined routinely once at four to five weeks postpartum, 5 to 20% of cows have PVD and 15 to 30% have subclinical endometritis (deBoer et al., 2014; Dubuc and Denis-Robichaud, 2017)

Cows with ketosis (blood beta-hydroxybutyrate (BHB) > 1.2 mmol/L) in both of the first two weeks postpartum had lower pregnancy rates at first artificial insemination (AI) than healthy cows, and cows with ketosis in either of the first two weeks had reduced pregnancy rates until ~ 165 days in milk (DIM; Walsh et al., 2007). Recent data (Rodriguez et al., 2021) refined the association by showing that ketotic cows in the lowest within-herd quartile of milk yield in the first week of lactation had substantially worse pregnancy rates, but cows with middle or top quartile milk yield had equally good pregnancy rates whether ketotic or not.

Many studies have consistently shown that cows with pus discharge (PVD) at four to six weeks postpartum have reduced probability of pregnancy at first AI (~15 to 25%) and take 20 to 30 days longer for half to become pregnant than healthy cows. Similarly, cows with chronic, low-grade uterine inflammation (endometritis diagnosed by uterine cytology) have median time to pregnancy 30 to 40 days longer than healthy cows. For details, see a systematic review by DeBoer et al. (2014).

It is clear that ketosis, PVD, and endometritis may have substantial harmful effects on the affected individual cows. An economic model (McArt et al., 2015) indicated that overall, herds with at least 15% of cows that experience ketosis would profit from a systematic test-and-treat program. A study of 17 herds in Ontario and Michigan found that all had ≥ 15% of cows with ketosis (Gordon et al., 2017), but some herds have a lower cumulative incidence (e.g., Rodriguez et al., 2021). A study of 126 farms in Quebec (Dubuc et Denis-Robichaud, 2017) helps to inform herd-level decisions about investing time and money in transition period monitoring programs to improve reproductive performance. The study estimated the prevalence of health conditions related to reproduction and their association with herd-level pregnancy at first insemination and with pregnancy losses from 30 to 60 days of gestation. The results are summarized in Table 1. The researchers identified thresholds of prevalence of health problems that were associated with pregnancy at first service below the top quartile in the sample of herds or with > 5% pregnancy loss. These data underline the importance of measuring the prevalence of these conditions in all herds, and suggest that where these exceed these levels, it is probably worth investing effort in prevention, detection, and treatment.

Table 1. Thresholds of prevalence of health conditions associated with reduced herd-level reproductive performance (from Dubuc and Denis-Robichaud, 2017)

Prevalence or Incidence (estimated from a sample of 20 cows per herd)	Threshold Associated With	
	First service probability of pregnancy < 40%	Pregnancy loss from 30 to 60 days > 5%
Retained placenta	-	≥ 5%
Ketosis*	≥ 12%	-
Displaced abomasum	≥ 4%	-
PVD at one month postpartum	≥ 5%	≥ 5%
Endometritis (uterine cytology examination)	≥ 19%	-
Anovulation (blood progesterone measured at 30-44 and 44-57 DIM)	≥ 21%	-

* Ketosis was measured only once per cow between one and 14 DIM, which is expected to underestimate the prevalence by approximately half; DIM = days in milk.

Figure 1 illustrates patterns seen in several large studies of the effects of uterine and non-uterine disease on reproduction. Cows with inflammatory disease are 5 to 15% points less likely to be pregnant to the first breeding and 5 to 10% points more likely to lose the pregnancy after diagnosis ≥ 30 days. Having more than one disease is worse than having a single clinical condition.

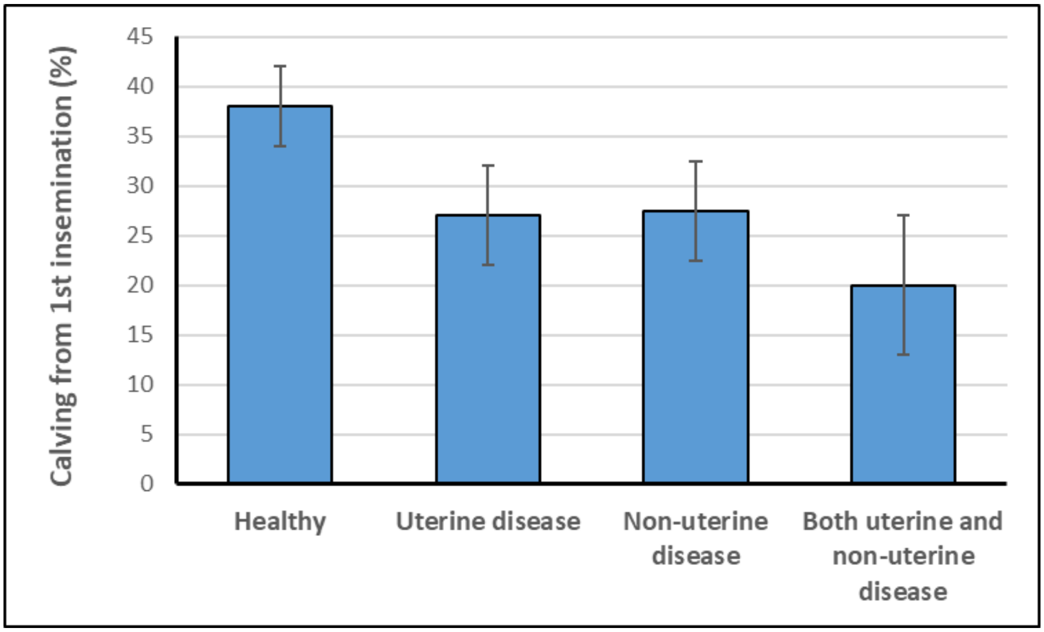

Figure 1. Associations of disease in the transition period with the probability of successful full-term pregnancy (mean and 95% confidence interval; data from 4476 cows; re-drawn from Ribeiro and Carvalho, 2017).

▪ Mechanisms Linking Heath and Reproduction

It makes intuitive sense that cows that experienced disease in the transition period have impaired reproductive performance. However, the mechanisms that connect transition disease to expression of estrus, pregnancy, and pregnancy losses at least one month to six or more months later are complex. These include:

- Final development of follicles from microscopic primary stages to a potentially ovulatory stage takes two to four months, so follicles ovulated for first service developed in the hormonal, energy deficit, and inflammatory environment of the postpartum period. The effects of these variables on follicle and oocyte quality are described in the "Britt hypothesis" (Britt, 1992).
- Follicular fluid and cells are exposed to endotoxin from uterine infection and inflammatory cytokines from the uterus (Bromfield et al., 2015) and affect follicular function and oocyte quality (Sheldon et al., 2019). The concentration of endotoxin in follicles was twice as great in anovular as ovular cows (Cheong et al., 2017).
- Postpartum uterine infection with recognized pathogenic bacteria was associated with reduced growth rate of the first dominant follicle, and after ovulation, with smaller corpora lutea (CL) with lesser blood progesterone concentration (Williams et al., 2007).
- Although metritis was not associated with anovulation (Ribeiro and Carvalho, 2017), endometritis in week five was associated with 1.5 times greater odds of anovulation at week nine postpartum (Dubuc et al., 2012).
- Cows that had metritis or another inflammatory condition postpartum were less likely to be pregnant and had fewer and lower quality embryos when flushed after first insemination (Gilbert, 2011; Ribeiro and Carvalho, 2017). Subclinical endometritis at the start of superovulation in donor cows reduced the number of transferable embryos by more than half (Carvalho et al., 2013).

- Embryos that were exposed to endotoxin in vitro (Magata and Shimizu, 2017) or to experimentally induced sterile inflammation in the cow (Hill and Gilbert, 2008) had reduced quality.

The interactions among these mechanisms and how they affect fertility was recently reviewed (Gilbert, 2019). Current understanding of this pathophysiology leads to the concept that it is important to have a rapid, robust, effective immune response immediately after calving, followed by regulation of inflammation that allows for return to normal reproductive function. Figure 2 illustrates the factors that contribute to this challenge.

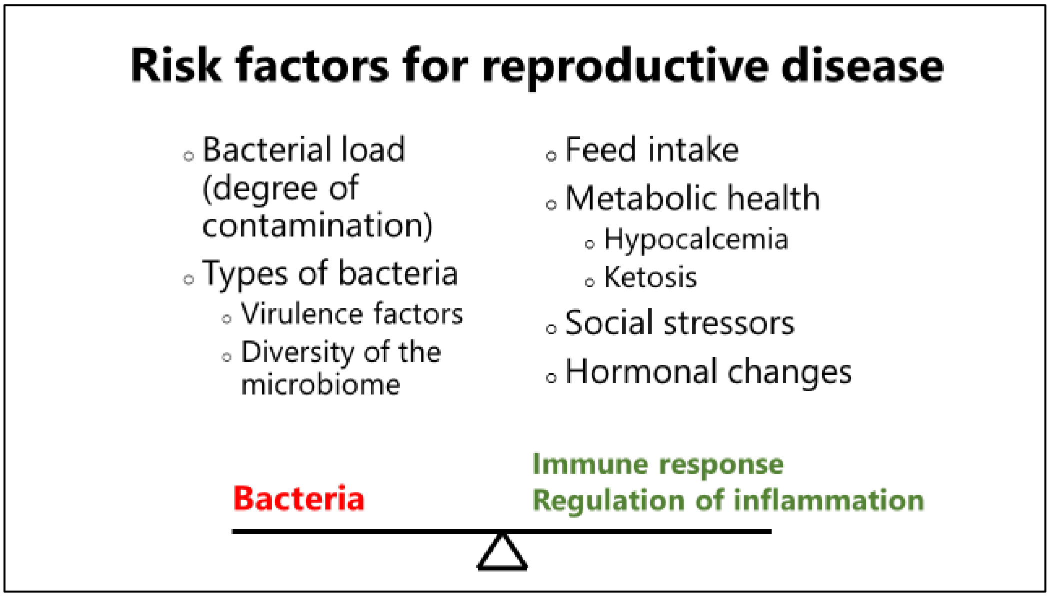

Figure 2. Risk factors for reproductive disease, which results from an imbalance between the load of bacterial pathogens and variables that support or impair effective and well-regulated response.

Adaptation or Maladaptation to Negative Energy Balance: NEFA and Ketosis

Cows must mobilize body fat and lose weight to support lactation. Increased blood concentrations of non-esterified fatty acids (NEFA; a marker of mobilization of fat) and ketones (notably BHB), a marker of oxidation of fatty acids) is part of the normal physiologic adaptation to lactation. However, if the amount or rate of fat mobilization exceeds the capacity of the liver to oxidize these fatty acids, the situation can become maladaptive, leading to increased risk of clinical disease.

Two indicators of adaptation to negative energy balance, NEFA and BHB, are associated with several aspects of immune function and systemic inflammation (Ingvartsen and Moyes, 2013; Pascottini and LeBlanc, 2020; LeBlanc 2020). About 35% of postpartum cows experience NEFA concentrations and 45% BHB concentrations above thresholds associated with increased risk of clinical disease, reduced milk yield, or impaired reproduction (McArt et al., 2013). Serum NEFA > 0.4 mmol/L in the ten days before calving is associated with increased risk of retained placenta, culling before 60 DIM, and reduced milk yield in the first four months of lactation. Subclinical ketosis (serum BHB ≥ 1.2 mmol/L) in the first or second week postpartum is associated with increased risk of metritis, endometritis, prolonged postpartum anovulation, and if onset is within five DIM, a reduction in milk yield in early lactation.

A detailed economic model (McArt et al., 2014) showed that a routine test-and-treat program for ketosis at least once in the first two weeks postpartum was profitable for herds with a cumulative incidence of ketosis (the proportion of cows that test positive at least once in the first two weeks) between 15 and 50%. That represents the majority of herds. The optimum program tests cows twice weekly between three and ten DIM. However, weekly testing is a good starting point.

Based on the results of two large randomized controlled trials (Gordon et al., 2017a,b) using cure of ketosis and milk yield in early lactation as endpoints, we recommend the following for treatment of ketosis:

- If blood BHB ≥ 1.2 but < 2.4 mmol (approximated by milk BHB of 100 μmol/L):
    - Treat with 300 g propylene glycol orally for 3 days
- If blood BHB ≥ 2.4 mmol/L (milk BHB of approximately 200 μmol/L):
    - Treat with 300 g propylene glycol orally for 5 days
- If blood BHB ≥ 1.2 mmol/L and blood glucose < 2.2 mmol/L (expected in 35 to 40% of ketotic cows):
    - Add injection of 25 ml Catosal or 1.25 mg vitamin B12 SC daily for 3 days
- Repeat testing after the final treatment. If blood BHB still ≥ 1.2 mmol/L, continue treatment with propylene glycol for 3 more days, once.
- Recent large studies do not support additional treatment with dexamethasone (Tatone et al., 2016) or IV dextrose (Capel et al., 2021).
- Once-a-day milking improved resolution of ketosis (Williamson et al., 2021) but the optimal duration of reduced milking frequency requires further study. In this trial, 14 days of 1X vs. 2X milking substantially improved cure of ketosis, especially in cows in first lactation, but milk yield was reduced through most of the lactation.

Herd Management to Support Health and Fertility

There are few validated nutritional or management tactics specifically to reduce reproductive disease or to improve reproductive performance. The aims are to support metabolic adaptation and innate immune function, thereby reducing the odds that inevitable inflammation and bacterial contamination of the uterus develop into disease. Excessive negative energy balance and fat mobilization (of which NEFA and BHB are markers), and prolonged insulin resistance contribute to systemic inflammation (Bradford et al., 2015) which may impair uterine and ovarian health (Gilbert, 2019). There is a healthy debate about whether systemic inflammation is a cause or a consequence of metabolic maladaptation, and how to define the latter (Horst et al., 2021). Practically, the goals remain to support metabolic health, immune function, and a regulated inflammatory state. A key element is to maintain feed intake around calving with a rapid increase afterwards. Although there is still much to be learned about the determinants of metabolic health and reproduction in dairy cows, best management practices for the transition period should minimize postpartum reproductive disease. These are summarized in Table 2.

Table 2. Recommended practices for management and monitoring of dairy cows in the transition period

Management

- Feed daily with 5% weighbacks
- Provide sufficient feeding space to minimize competition (≥ 30” (75 cm) per cow or no more than 4 cows per 5 headlocks). Therefore, design transition pens for ~ 130% of the expected monthly average number of calvings.
- ≤ 85% freestall stocking density
- 130 ft^2 (12 m^2) of bedded pack/cow
- Stalls sized and bedded for cow comfort; heifers exposed to freestalls and headlocks before the transition pen.
- Fans and sprinklers when the temperature-humidity index is > 68 (~ > 25^{o}C)
- House heifers separately if it does not violate any of the above.
- Moderate BCS at calving: 3.0 to 3.5

Nutrition

- Do not exceed energy requirements in the dry period
- Provide sufficient metabolizable protein (~1100 g/d)
- Allow time for adaptation to dietary changes (3 to 4 weeks) or use single dry cow diet
- Minimize group and diet changes
    - Move cows into new groups at least 2 at a time
- Provide water ad lib: 2 sources per pen and ≥ 4” (10 cm) of linear trough space per cow
- Feed dietary vitamin E at 1000 IU in far-off and 2000 IU per cow per day in the close-up periods, and 0.3 ppm selenium (ideally ~ 6 mg/cow/day))
- DCAD ~ -100mEq/kg DM for 3 weeks before calving; target urine pH between 6.0 and 6.5
- Monensin capsules

Monitoring

- Measure dry matter intake daily
- Measure forage dry matter weekly and adjust rations accordingly
- Blood testing as needed
- NEFA < 0.4 mmol/L in the week before calving (week -1); < 1.0 mmol/L in the first week of lactation
- BHB < 0.8 mmol/L in week -1
- BHB < 1.1 mmol/L in week 1
- BHB < 1.2 mmol/L in weeks 2 and 3
- Calcium: 1st lactation cows: > 2.15 mmol/L at 1 and 2 DIM; multiparous cows: > 1.8 mmol/L at 1 DIM* and > 2.2 mmol/L at 4 DIM. *for disease risk; cows with serum calcium < 1.8 at 1 DIM but > 2.2 at 4 DIM had greater milk yield (McArt & Neves, 2020).

▪ Conclusion

Monitoring of dairy herds should include quantitative assessment of the management and nutritional practices in Table 2, the incidence of ketosis and metritis, and the prevalence of PVD. These data will inform the development of herd-specific plans and decisions about routine testing programs. Armed with these data, advisors and producers can identify potential problems and opportunities to support success at first insemination.

▪ References

Bradford, B., K. Yuan, J. Farney, L. Mamedova, and A. Carpenter. 2015. Invited review: Inflammation during the transition to lactation: New adventures with an old flame. J. Dairy Sci. 98:6631-6650.

Britt, J.H. 1992. Impacts of early postpartum metabolism on follicular development and fertility. Bovine Proc. 24:39-43.

Bromfield, J.J., J.E.P. Santos, J. Block, R.S. Williams and M. Sheldon. 2015. Physiology and Endocrinology Symposium: Uterine infection: Linking infection and innate immunity with infertility in the high-producing dairy cow. J. Anim. Sci. 93:2021-2033.

Capel, M.B., K.D. Bach, S. Mann, and J.A.A. McArt. 2021. A randomized controlled trial to evaluate propylene glycol alone or in combination with dextrose as a treatment for hyperketonemia in dairy cows. J. Dairy Sci. 104:2185-2194. doi: 10.3168/jds.2020-19111.

Carvalho, P.D., A.H. Souza, R. Sartori, K.S. Hackbart, A.R. Dresch, L.M. Vieira, P.S. Baruselli, J.N. Guenther, P.M. Fricke, R.D. Shaver, and M.C. Wiltbank. 2013. Effects of deep-horn AI on fertilization and embryo production in superovulated cows and heifers. Theriogenology. 80:1074-1081.

Carvalho, M.R., F. Peñagaricano, J.E.P. Santos, T.J. DeVries, B.W. McBride, and E.S. Ribeiro. 2019. Long-term effects of postpartum clinical disease on milk production, reproduction, and culling of dairy cows. J Dairy Sci. 102:11701-11717. doi: 10.3168/jds.2019-17025.

Cheong, S.H., O.G. Sa Filho, V.A. Absalon-Medina, A. Schneider, W.R. Butler, and R.O Gilbert. 2017. Uterine and systemic inflammation influences ovarian follicular function in postpartum dairy cows. PLoS One 12: e0177356.

de Boer, M.W., S.J. LeBlanc, J. Dubuc, S. Meier, W. Heuwieser, S. Arlt, R.O. Gilbert, and S. McDougall. 2014. Invited review: systematic review of diagnostic tests for reproductive-tract infection and inflammation in dairy cows. J Dairy Sci. 97:3983-3999.

Dubuc, J., T.F. Duffield, K.E. Leslie, J.S. Walton, and S.J. LeBlanc. 2012. Risk factors and effects of postpartum anovulation in dairy cows. J. Dairy Sci. 95:1845-1854.

Dubuc, J. and J.A. Denis-Robichaud. 2017. A dairy herd-level study of postpartum diseases and their association with reproductive performance and culling. J. Dairy Sci. 100:3068-3078.

Gilbert, R.O. 2011. The effects of endometritis on the establishment of pregnancy in cattle. Reprod. Fertil. Dev. 24:252–257.

Gilbert, R.O. 2019. Symposium review: Mechanisms of disruption of fertility by infectious diseases of the reproductive tract. J. Dairy Sci. 102:3754-3765.

Gordon, J.L., T.F. Duffield, T.H. Herdt, D.F. Kelton, L. Neuder, and S.J. LeBlanc. 2017. Effects of a combination butaphosphan and cyanocobalamin product and insulin on ketosis resolution and milk production J. Dairy Sci. 100:2954-2966.

Gordon, J.L., S.J. LeBlanc, D.F. Kelton, T.H. Herdt, L. Neuder, and T.F. Duffield. 2017. Randomized clinical field trial on the effects of butaphosphan-cyanocobalamin and propylene glycol on ketosis resolution and milk production. J. Dairy Sci. 100:3912-3921.

Hill, J. and R. Gilbert. 2008. Reduced quality of bovine embryos cultured in media conditioned by exposure to an inflamed endometrium. Aust. Vet. J. 86:312-316.

Horst, E.A., S.K. Kvidera, and L.H. Baumgard. 2021. Invited review: The influence of immune activation on transition cow health and performance - A critical evaluation of traditional dogmas. J Dairy Sci. 104:8380-8410. doi: 10.3168/jds.2021-20330.

Ingvartsen, K.L. and K.M. Moyes. 2013. Nutrition, immune function and health of dairy cattle. Animal. 7:112-122.

LeBlanc, S.J. 2020. Review: relationships between metabolism and neutrophil function in dairy cows in the peripartum period. Animal. 14:S1:s44–s54.

Magata, F. and T. Shimizu. 2017. Effect of lipopolysaccharide on developmental competence of oocytes. Reprod. Toxicol. 71:1-7.

McArt, J.A.A., D.V. Nydam, and G.R. Oetzel. 2013. Elevated non-esterified fatty acids and β-hydroxybutyrate and their association with transition dairy cow performance. The Vet. J. 198:560-570.

McArt, J.A.A., D. V. Nydam, G.E. Oetzel, and C.L. Guard. 2014. An economic analysis of hyperketonemia testing and propylene glycol treatment strategies in early lactation dairy cattle. Prev. Vet. Med. 117: 170-179.

McArt, J.A.A. and R.C. Neves. 2020. Association of transient, persistent, or delayed subclinical hypocalcemia with early lactation disease, removal, and milk yield in Holstein cows. J Dairy Sci. 103:690-701. doi: 10.3168/jds.2019-17191.

Pascottini, O.B. and S.J. LeBlanc. 2020. Modulation of immune function in the bovine uterus peripartum. Theriogenology. 150:193-200.

Ribeiro, E.S. and M.R. Carvalho. 2017. Impact and mechanisms of inflammatory diseases on embryonic development and fertility in cattle. Anim. Reprod. 14:589-600.

Santos, J.E.P., R.S. Bisinotto, E.S. Ribeiro, F.S. Lima, L.F. Greco, C.R. Staples, and W.W. Thatcher. 2010. Applying nutrition and physiology to improve reproduction in dairy cattle. Soc. Reprod. Fertil. Suppl. 67:387-403.

Sheldon, I.M., J.G. Cronin, and J.J. Bromfield. 2019. Tolerance and innate immunity shape the development of postpartum uterine disease and the impact of endometritis in dairy cattle. Annual Rev. Anim. Biosci. 15:361-384

Tatone, E.H., T.F. Duffield, M.B. Capel, T.J. DeVries, S.J. LeBlanc, and J.L. Gordon. 2016. A randomized controlled trial of dexamethasone as an adjunctive therapy to propylene glycol for treatment of hyperketonemia in postpartum dairy cattle. J. Dairy Sci. 99:8991–9000.

Walsh R.B., J.S. Walton, D.F. Kelton, S.J.LeBlanc., K.E.Leslie, and T.F. Duffield. 2007. The effect of subclinical ketosis in early lactation on reproductive performance of postpartum dairy cows. J Dairy Sci. 90:2788-2796.

Williams, E.J., D.P. Fischer, D.E. Noakes, G.C.W. England, A. Rycroft, H. Dobson, and I.M Sheldon. 2007. The relationship between uterine pathogen growth density and ovarian function in the postpartum dairy cow. Theriogenology. 68:549-559.

Williamson, M., R. Couto Serrenho, B.W. McBride, S.J. LeBlanc, T.J. DeVries, and T.F. Duffield. 2022. Reducing milking frequency from twice to once daily as an adjunct treatment for ketosis in lactating dairy cows - A randomized controlled trial. J. Dairy Sci. 105:1402-1417.


Farm On
CANADA
For farming life.™
Masterfeeds®
an Alltech® company
Your business is life.
When your business – your product – is life, the stakes are high.
Production improvement, herd growth and development, and continuously raising the performance results bar drives everything we do. Masterfeeds is focused on dairy production success.
You farm life – we're here to help you with farming life.
We are dairy specialists. Let us run through the options for better Nutrition Management with you.
Fernando Hernandez 403-915-4311 fhernandez@masterfeeds.com
Wayne Kaplar 403-315-0063 wkaplar@masterfeeds.com
Hamid Khazanehei, PhD 403-437-3763 hkhazanehei@masterfeeds.com
Kyle Macor 403-795-9018 kmacor@masterfeeds.com
Mark Schokking 403-596-8582 mschokking@masterfeeds.com
Brian Tolley 587-370-7917 btolley@masterfeeds.com


#63
JAY-LOR
JAY-LOR
BECAUSE NUTRITION MATTERS.