Minimizing Inflammation in Transition Cows

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Abstract

Inflammation biology has been a focus of intense research in both the biomedical and animal sciences in the past two decades. This work has revealed that inflammation is critically important in the immune response to pathogens, but it also integrated with many other aspects of physiology. The transition dairy cow makes an excellent case study for this. In addition to needing to be prepared for mastitis and metritis challenges, the cow utilizes inflammatory signals and cells to drive the calving process. Inflammatory signaling molecules, though, are not well contained in specific tissues, resulting in systemic responses. These responses can include suppression of feed intake and milk synthesis. Ongoing research has demonstrated that added inflammatory challenges impair intake and milk production in transition cows, whereas several anti-inflammatory strategies have dramatically increased whole-lactation milk yield. Inflammatory signaling is therefore central to the interactions of health, productivity, and nutrition in the transition period, with important impacts on the entire lactation.

Introduction

Dairy producers and those who advise them are well aware of the challenges that face cows during the transition to lactation. The 2 to 3 week period after calving typically accounts for 40 to 50% of health problems on a dairy, and high cull rates in early lactation are a costly problem for many farms. Research has generated strong evidence that part of the problem during this time is altered immune function and inflammation during the transition period. This immune dysfunction occurs at a time when nearly all cows experience some degree of inflammation, which is somewhat counter-intuitive given that inflammation is a critical tool for immune system activation. Furthermore, measures of immune function and inflammation are predictive of disease incidence in dairy cows, suggesting that changes to support immune function and to limit inflammation may improve the well-being and productivity of cows. We'll explore this evidence and consider whether strategies to push back against postpartum inflammation are beneficial to health and productivity.

What's the Evidence for an Inflammatory State Around Calving?

Although body temperature is often slightly elevated for a few days after calving, the inflammation that is detected in transition cows doesn't necessarily include the traditional pain, fever, and edema responses associated with acute inflammation. Instead, transition inflammation is generally subclinical, marked by increases in signals in the bloodstream released by tissues in response to inflammatory stressors (Bradford et al., 2015).

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Beginning nearly 20 years ago, several research groups began asking questions about whether transition cow disease complexes could have an underlying cause associated with excessive inflammation. In Italy, Giuseppe Bertoni and colleagues began documenting increased concentrations of circulating inflammatory biomarkers in cows through the transition period, and further showed that biomarkers were most elevated in cows that ended up suffering from transition disorders (Bertoni et al., 2008). In some cases, these markers were clearly altered before disease onset, suggesting that they were predictive of a disease orientation, rather than a response to the disease itself.

More recently, groups in several countries have carried out large-scale epidemiological studies to investigate whether elevated inflammatory biomarkers are associated with subsequent problems. These studies have focused heavily on the acute phase protein haptoglobin, which is produced by the liver when oxidative stress, immune system inflammatory signals, or signs of infectious agents trigger inflammatory gene expression. Plasma concentrations of haptoglobin greater than 1.1 g/L were associated with a 947 kg decrease in 305-day mature equivalent milk yield, and primiparous cows with haptoglobin >1.3 g/L in the first week post-calving had a 42% decreased risk of conception during the first 150 days in milk (Huzzey et al., 2015). On day 3 postpartum, a cutoff of 0.15 g/L separated healthy cows from those who had transition disorders (Qu et al., 2014). A day 3 cutoff of 0.6 g/L offered the best balance of specificity and sensitivity for detection of mastitis (Huzzey et al., 2009). Cows with haptoglobin > 0.46 g/L on d 2 to 8 postpartum took longer to become pregnant (Nightingale et al., 2015). Although there is variability across studies in cutoff values, elevated postpartum haptoglobin concentrations were consistently linked to impaired productivity, fertility, and health.

Much of the evidence around transition inflammation is based on acute phase proteins, but recently investigation of other signals has validated the conclusion that most transition cows experience some degree of systemic inflammation. Concentrations of inflammatory cytokines generally appear to decline after calving, but they remain elevated in cows with health problems. Furthermore, oxylipids – a key class of lipid signals that can promote or resolve inflammation – shift to a more pro-inflammatory profile in the days immediately after calving (Yuan et al., 2013). Finally, oxidative balance is often challenged after calving, and oxidative stress can provide a link between suboptimal metabolism and inflammatory signaling (Sordillo and Mavangira, 2014).

At a minimum, the liver shows signs of a subclinical inflammatory state in the week after calving. However, given the other signals that are also changed in the bloodstream and in tissues that have been sampled, it appears that most cows experience a mild systemic inflammatory state at this time (Bradford et al., 2015).

Physiological Roles for Inflammation in the Transition Cow

Inflammatory cascades are involved in many disease processes, from bacterial infections to arthritis to cancer. It's easy enough, then, to associate any inflammatory signal with negative outcomes. However, it's important to also recognize that inflammatory signaling exists for good reasons, and it plays a critical role in many biological processes. Most predictably, inflammation is an essential component of the immune response, particularly for bacterial infections. However, inflammation is also used

for tasks unrelated to immunity. For example, deleting certain components of inflammatory signaling cascades in the mammary gland completely disrupts mammary development in mice, resulting in an inability to secrete milk after parturition (Cao et al., 2001).

The process of giving birth is driven, to a large extent, by inflammatory signals. As the fetus nears term, the hormonal cross-talk with the dam triggers local signaling in the uterus and cervix that attracts circulating immune cells into these tissues (Van Engelen et al., 2009). The additional inflammatory molecules produced by these cells begin to drive important changes, including degradation of connective tissue in the cervix (cervical ripening), and as parturition begins, contraction of the myometrium.

The best demonstration of the importance of inflammation in parturition is the study carried out by Newby et al. (2017). Seeking to combat the subtle fever and the poor appetite common to many fresh cows, this team first tested the impact of giving flunixin meglumine (a non-steroidal anti-inflammatory drug) to cows several hours before calving and again in the day after calving. However, this treatment resulted in a severe increase in stillbirth rate (26.5% vs. 5.3% in controls) and had to be stopped early. To avoid risk of stillbirth, Newby and colleagues then tested administration of flunixin at 2 and 24 hours after calving. Unfortunately, this treatment also had unintended consequences, this time causing a 2.6-fold increase in the risk of retained placenta. The increase in retained placenta, in turn, significantly increased metritis risk. Although frustrating, this study made an important contribution by demonstrating in the cow that systemic anti-inflammatory drugs can suppress inflammatory signaling to the point of derailing normal parturition. Clearly, we cannot view inflammation as being always negative.

Inflammatory Consequences After Calving

Despite the necessary role for inflammatory signals at parturition, association studies discussed above point to negative outcomes in cows with relatively high blood biomarkers of inflammation. So what are the impacts of increasing inflammation after calving? We administered a very low dose of the inflammatory cytokine tumor necrosis factor α (TNFα) for the first 7 days of lactation to assess the impact of a subtle increase in postpartum inflammation (Yuan et al., 2013). Although our treatment did not induce any of the classical physiological signs of acute inflammation, we did observe significant increases in circulating mediators of inflammation, validating our approach to enhancing sub-acute inflammation. During the week of treatment, TNFα decreased feed intake by 18% and energy-corrected milk yield by 17%, with no change in energy balance. Furthermore, in the highest TNFα treatment group, 7 of 11 cows were diagnosed with at least one subclinical transition disorder, compared to just 2 of 11 in the control group. Along with a few other studies that have directly induced inflammation in the transition period (Trevisi et al., 2009), these findings demonstrate a causative role of inflammation in at least some common problems in early lactation.

Negative impacts of inflammatory signals on milk synthesis have been consistently reported. For example, sterile inflammation induced by lipopolysaccharide (endotoxin) can cause dramatic impairment of pathways driving synthesis of nearly all milk components. Endotoxin significantly decreased transcript abundance of glucose transporters, fatty acid binding protein 3, and carnitine transporters in rat mammary tissue (Ling and Alcorn, 2010) and induced similar suppression of transcripts for fatty acid synthesis proteins, potassium channels, and carbohydrate metabolism enzymes

in mouse mammary tissue (Zheng et al., 2006). The net effect of inflammatory down-regulation of nutrient transporters and synthetic enzymes (and probably other undiscovered mechanisms) is that secretion of all major milk components is suppressed by the severe inflammation induced by endotoxin in the dairy cow (Oliver and Calvinho, 1995; Ballou, 2012).

One question that has not yet been addressed in observational studies is whether the pattern of inflammation impacts long-term outcomes. We hypothesize that brief spikes in inflammatory signals that are resolved in the first 3 to 4 days of lactation may aid in physiological adaptations to lactation and the end of pregnancy. However, failure to rapidly resolve these signals may lead to a variety of adverse impacts that ultimately impair productivity, health, and fertility (Figure 1).

Responses to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

To address whether normal transition inflammation is a problem, a variety of labs have used NSAIDs to treat postpartum inflammation. In a study, Bertoni et al. (2004) treated 11 cows/treatment with lysine acetyl-salicylate (aspiri) or for the first 5 days postpartum and monitored milk production through day 126 of lactation. Peak milk yield tended to increase with aspirin treatment ($P < 0.10$). The same group subsequently conducted a similar study with 23 cows/treatment and found that aspirin treatment over the first 5 days of lactation increased milk yield through day 60 of lactation ($P < 0.05$), with a 13% increase in peak milk yield (Trevisi and Bertoni, 2008).

Motivated by these promising findings, we conducted a study with 78 cows assigned to either control or sodium salicylate delivered via drinking water (2 g/L) for the first 7 days of lactation. At first, the results did not look very promising – salicylate decreased blood glucose and increased ketone concentrations in early lactation, with no increase in early milk yield (Farney et al., 2013a). However, as lactation progressed, the oldest cohort of cows treated with salicylate (those in parity 3 and greater) responded by producing 21% more milk over the full lactation, and fully 30% more milk fat, than parity-matched controls (Farney et al., 2013b). On the other hand, primiparous cows treated with salicylate tended to produce less milk, suggesting a potential parity difference in either baseline inflammatory status or response to inflammatory signals.

We subsequently completed a follow-up study to evaluate whether postpartum treatment of multiparous cows could increase whole-lactation productivity of cows on a commercial farm. To facilitate treatment in a commercial setting, we shortened the postpartum treatment to 3 days (sodium salicylate) or 1 day (meloxicam) and compared them to placebo treatments (Carpenter et al., 2016) across 153 cows. Despite this very limited treatment window, cows treated with either NSAID produced 7 to 9% more milk over the whole lactation compared to placebo.

Barragan and colleagues (2020a) recently published responses to a 2-day treatment regimen with aspirin rather than sodium salicylate. This strategy, like previous work with salicylate, showed no impacts on milk production of first-lactation cows, but in multiparous cows, aspirin caused a 4% increase in milk yield during the first 60 days in milk. However, no difference in 305-day milk yield was detected.

Swartz and colleagues (2018) evaluated responses to treatment with meloxicam either ~24 hours before calving or within 12 hours after calving. Both treatments increased milk yield over the first 15 weeks of lactation, but the

benefit was greater for the pre-calving treatment (+18%) than the post-calving treatment (+7%). In addition to revealing exciting milk responses, the pre-calving treatment with meloxicam did not cause problems with calving or increase retained placenta incidence, in agreement with another recent study (Newby et al., 2014). Contrary to the authors' expectations, however, meloxicam did not benefit cows experiencing dystocia – in fact, it appeared to improve milk yield only in cows that did not experience dystocia (Swartz et al., 2018). This is puzzling, given that dystocia is associated with increased inflammation, but perhaps it can be explained by the single treatment being inadequate to impact the greater inflammatory pressure in these cows. On the other hand, a very recent publication showed that aspirin treatment of organically managed cows improved milk yield of dystotic, but not eutotic, cows (Barragan et al., 2020b).

We (Carpenter et al., 2018) and several other groups have failed to observe significant impacts of postpartum NSAID treatment on milk yield in some studies, and it remains to be seen whether a treatment paradigm can be found that is consistently effective. However, we believe that impacts on long-term milk yield likely require treatment before or early after calving and that effects are not likely to be obvious before 60 days in milk. We speculate that herds with relatively high inflammatory biomarkers may be more responsive to these strategies, and there is good evidence that herd-to-herd variation in haptoglobin is substantial (Nightingale et al., 2015).

A few studies have evaluated health impacts following blanket treatment with NSAID after parturition. In general, there has been little evidence of overall improvements in health or decreased risk of culling following early lactation NSAID treatment (Farney et al., 2013b; Meier et al., 2014; Swartz et al., 2018; Barragan et al., 2020a). In fact, one small study suggested possible increased risk of infections after NSAID treatment (Bertoni et al., 2004). However, our commercial farm study generated some intriguing results (Carpenter et al., 2016). Over the 365 days following treatment, meloxicam tended to delay removal from the herd based on survival analysis ($P = 0.06$; 30, 35, and 38 cows of 51 enrolled remained in the herd at 365 days post-calving for control, salicylate, and meloxicam, respectively). Meloxicam primarily decreased early-lactation culling, and health events recorded by the farm suggested that metabolic disorders accounted for most of this decrease. More research is necessary to determine whether blanket treatment of postpartum cows can really decrease culling risk.

Nutritional Anti-Inflammatory Strategies

In the United States, the NSAID strategies outlined above do not currently have regulatory approval. However, several nutrient classes offer the ability to shift cellular function in an anti-inflammatory direction. For example, omega-3 fatty acids (if they can be delivered past the rumen) activate a cellular receptor that inhibits inflammatory signaling, in addition to serving as substrates for the production of anti-inflammatory oxylipids. Polyphenols are another very large class of compounds that often have antioxidant and anti-inflammatory effects on animals (Olagaray and Bradford, 2019), although little controlled research has evaluated impacts of dietary polyphenols on inflammatory status of dairy cattle.

We recently published a study evaluating an extract from Chinese skullcap (*Scutellaria baicalensis*) for its impacts on early lactation dairy cows (Olagaray et al., 2019). The extract was supplied (or not) via an automated milking system, providing the supplement for either 5 or 60 days post-calving. Although the 5-day

treatment did not significantly alter the lactation curve, the 60-day treatment increased whole-lactation milk yield by 13% over controls.

This study did not identify the mode of action of the Chinese skullcap extract, but the response curve closely mirrored temporal patterns of response to NSAIDs in previous studies (Farney et al., 2013b; Carpenter et al., 2016), with little or no response to treatment in the first month of lactation, following by a separation of treatments from week 6 through peak lactation, and maintaining that benefit through the end of lactation. This response time course can be difficult to explain, particularly follow a single dose of an NSAID in the day around calving. To begin to ascertain how this might occur, we visualized expected responses to shifts in cell growth, death, and function (Figure 2). The observed responses to the plant extract and NSAIDs appear to be most consistent with an increase in secretory cell productivity (milk synthesis per cell) rather than a change in secretory cell number. Preliminary findings from mammary biopsies support this conclusion.

Why would secretory cell activity change for an entire lactation following an early lactation anti-inflammatory strategy? This remains an open question, but preliminary findings point to potential impacts on epigenetics, which is the modification of DNA in a manner that alters gene expression in a sustained manner. We hypothesize that the mammary gland may be in an "epigenetic rewriting" state at the onset of lactation, making short-term treatments potentially impactful for many months. These ideas remain under investigation, with many candidate bioactive nutrients ripe for study.

Conclusions

The story behind the transition cow and her many challenges remains complicated, but progress in the past 20 years has firmly established inflammatory signaling in multiple organ systems as a part of the puzzle. Most cows experience at least mild systemic inflammation after calving, potentially derived from the calving process itself. The healthiest cows resolve that inflammatory state quickly, but a significant subset of cows shows elevated inflammatory markers for weeks after calving, likely contributing to issues such as poor feed intake, liver function problems, and low peak production. Reponses to both non-steroidal anti-inflammatory drugs and bioactive polyphenol feed additives have significantly increased whole-lactation milk yield, suggesting that inflammatory pathways have an important impact on mammary function. Therefore, minimizing postpartum inflammation represents an extremely promising avenue for enhancing dairy efficiency in a manner that also supports transition cow health.

References

Ballou, M.A. 2012. Growth and Development Symposium: Inflammation: Role in the etiology and pathophysiology of clinical mastitis in dairy cows. J. Anim. Sci. 90:1466–1478. doi:10.2527/jas.2011-4663.

Barragan, A.A., L. Bauman, L. da Costa, J. Velez, J.D.R. Gonzalez, G.M. Schuenemann, B. Menichetti, J. Piñeiro, and S. Bas. 2020b. Administration of acetylsalicylic acid after parturition in lactating dairy cows under certified organic management: Part I. Milk yield, milk components, activity patterns, fertility, and health. J. Dairy Sci. 103:11697–11712. doi:10.3168/jds.2020-18388.

Barragan, A.A., E. Hovingh, S. Bas, J. Lakritz, L. Byler, A. Ludwikowski, S. Takitch, J. Zug, and S. Hann. 2020a. Effects of postpartum acetylsalicylic acid on metabolic status, health, and production in lactating dairy cattle. J. Dairy Sci. 103:8443–8452. doi:10.3168/jds.2019-17966.

Bertoni, G., E. Trevisi, and A. Ferrari. 2008. The APP changes at calving time in dairy cows: Meaning and prognostic relevance. 7th Int. Meet. Acute Phase Proteins 181–183.

Bertoni, G., E. Trevisi, and F. Piccioli-Cappelli. 2004. Effects of acetyl-salicylate used in post-calving of dairy cows. Vet. Res. Commun. 28:217–219.

Bradford, B.J., K. Yuan, J.K. Farney, L.K. Mamedova, and A.J. Carpenter. 2015. Invited review: Inflammation during the transition to lactation: New adventures with an old flame. J. Dairy Sci. 98:6631–6650. doi:10.3168/jds.2015-9683.

Cao, Y., G. Bonizzi, T.N. Seagroves, F.R. Greten, R. Johnson, E. V Schmidt, and M. Karin. 2001. IKKα provides an essential link between RANK signaling and cyclin D1 expression during mammary gland development. Cell 107:763–775. doi:http://dx.doi.org/10.1016/S0092-8674(01)00599-2.

Carpenter, A.J., C.M. Ylioja, L.K. Mamedova, K.E. Olagaray, and B.J. Bradford. 2018. Effects of early postpartum sodium salicylate treatment on long-term milk, intake, and blood parameters of dairy cows. J. Dairy Sci. 101:1437–1447. doi:https://doi.org/10.3168/jds.2017-13057.

Carpenter, A.J., C.M. Ylioja, C.F. Vargas, L.K. Mamedova, L.G. Mendonca, J.F. Coetzee, L.C. Hollis, R. Gehring, and B.J. Bradford. 2016. Hot topic: Early postpartum treatment of commercial dairy cows with nonsteroidal antiinflammatory drugs increases whole-lactation milk yield. J Dairy Sci 99:672–679. doi:10.3168/jds.2015-10048.

Farney, J.K., L.K. Mamedova, J.F. Coetzee, B. KuKanich, L.M. Sordillo, S.K. Stoakes, J.E. Minton, L.C. Hollis, and B.J. Bradford. 2013a. Anti-inflammatory salicylate treatment alters the metabolic adaptations to lactation in dairy cattle. Am. J. Physiol. Integr. Comp. Physiol. 305:R110–R117. doi:10.1152/ajpregu.00152.2013.

Farney, J.K., L.K. Mamedova, J.F. Coetzee, J.E. Minton, L.C. Hollis, and B.J. Bradford. 2013b. Sodium salicylate treatment in early lactation increases whole-lactation milk and milk fat yield in mature dairy cows. J. Dairy Sci. 96:7709–7718.

Huzzey, J.M., T.F. Duffield, S.J. LeBlanc, D.M. Veira, D.M. Weary, and M.A.G. von Keyserlingk. 2009. Short communication: Haptoglobin as an early indicator of metritis. J. Dairy Sci. 92:621–625. doi:10.3168/jds.2008-1526.

Huzzey, J.M., S. Mann, D. V Nydam, R.J. Grant, and T.R. Overton. 2015. Associations of peripartum markers of stress and inflammation with milk yield and reproductive performance in Holstein dairy cows. Prev. Vet. Med. 120:291–297. doi:10.1016/j.prevetmed.2015.04.011.

Ling, B., and J. Alcorn. 2010. LPS-induced inflammation downregulates mammary gland glucose, fatty acid, and L-carnitine transporter expression at different lactation stages. Res. Vet. Sci. 89:200–202. doi:10.1016/j.rvsc.2010.03.004.

Meier, S., N. V Priest, C.R. Burke, J.K. Kay, S. McDougall, M.D. Mitchell, C.G. Walker, A. Heiser, J.J. Loor, and J.R. Roche. 2014. Treatment with a nonsteroidal antiinflammatory drug after calving did not improve milk production, health, or reproduction parameters in pasture-grazed dairy cows. J. Dairy Sci. 97:2932–2943. doi:10.3168/jds.2013-7838.

Newby, N.C., K.E. Leslie, H.D.P. Dingwell, D.F. Kelton, D.M. Weary, L. Neuder, S.T. Millman, and T.F. Duffield. 2017. The effects of periparturient administration of flunixin meglumine on the health and production of dairy cattle. J. Dairy Sci. 100:582–587. doi:10.3168/jds.2016-11747.

Newby, N.C., D. Renaud, R. Tremblay, and T.F. Duffield. 2014. Evaluation of the effects of treating dairy cows with meloxicam at calving on retained fetal membranes risk. Can. Vet. J. 55:1196–1199. doi:10.1186/1746-6148-9-211.4.

Nightingale, C.R., M.D. Sellers, and M.A. Ballou. 2015. Elevated plasma haptoglobin concentrations following parturition are associated with elevated leukocyte responses and decreased subsequent reproductive efficiency in multiparous Holstein dairy cows. Vet. Immunol. Immunopathol. 164:16–23. doi:10.1016/j.vetimm.2014.12.016.

Olagaray, K.E., and B.J. Bradford. 2019. Plant flavonoids to improve productivity of ruminants – A review. Anim. Feed Sci. Technol. 251:21–36. doi:https://doi.org/10.1016/j.anifeedsci.2019.02.004.

Olagaray, K.E., M.J. Brouk, L.K. Mamedova, S.E. Sivinski, H. Liu, F. Robert, E. Dupuis, M. Zachut, and B.J. Bradford. 2019. Dietary supplementation of Scutellaria baicalensis extract during early lactation decreases milk somatic cells and increases whole lactation milk yield in dairy cattle. PLoS One 14:e0210744.

Oliver, S.P., and L.F. Calvinho. 1995. Influence of inflammation on mammary gland metabolism and milk composition. J. Anim. Sci. 73:18–33. Pollott, G.E. 2004. Deconstructing milk yield and composition during lactation using biologically based lactation models. J. Dairy Sci. 87:2375–2387.

Qu, Y., A.N. Fadden, M.G. Traber, and G. Bobe. 2014. Potential risk indicators of retained placenta and other diseases in multiparous cows. J. Dairy Sci. 97:4151–4165. doi:10.3168/jds.2013-7154.

Sordillo, L.M., and V. Mavangira. 2014. The nexus between nutrient metabolism, oxidative stress and inflammation in transition cows. Anim. Prod. Sci. 54:1204–1214. doi:http://dx.doi.org/10.1071/AN14503.

Swartz, T.H., H.H. Schramm, J.M. Bewley, C.M. Wood, K.E. Leslie, and C.S. Petersson-Wolfe. 2018. Meloxicam administration either prior to or after parturition: Effects on behavior, health, and production in dairy cows. J. Dairy Sci. 101:10151–10167. doi:10.3168/jds.2018-14657.

Trevisi, E., M. Amadori, A.M. Bakudila, and G. Bertoni. 2009. Metabolic changes in dairy cows induced by oral, low-dose interferon-alpha treatment. J. Anim Sci. 87:3020–3029. doi:10.2527/jas.2008-1178.

Trevisi, E., and G. Bertoni. 2008. Attenuation with acetylsalicylate treatments of inflammatory conditions in periparturient dairy cows. P.I. Quinn, ed. Nova Science Publishers, Hauppauge, NY.

Van Engelen, E., M.W. De Groot, V.N.A. Breeveld-Dwarkasing, M.E. Everts, G.C. Van Der Weyden, M.A.M. Taverne, and V.P.M.G. Rutten. 2009. Cervical ripening and parturition in cows are driven by a cascade of pro-inflammatory cytokines. Reprod. Domest. Anim. 44:834–841. doi:10.1111/j.1439-0531.2008.01096.x.

Yuan, K., J.K. Farney, L.K. Mamedova, L.M. Sordillo, and B.J. Bradford. 2013. TNFα altered inflammatory responses, impaired health and productivity, but did not affect glucose or lipid metabolism in early-lactation dairy cows. PLoS One 8:e80316. doi:10.1371/journal.pone.0080316.

Zheng, J., A. Watson, and D. Kerr. 2006. Genome-wide expression analysis of lipopolysaccharide-induced mastitis in a mouse model. Infect. Immun. 74:1907–1915.

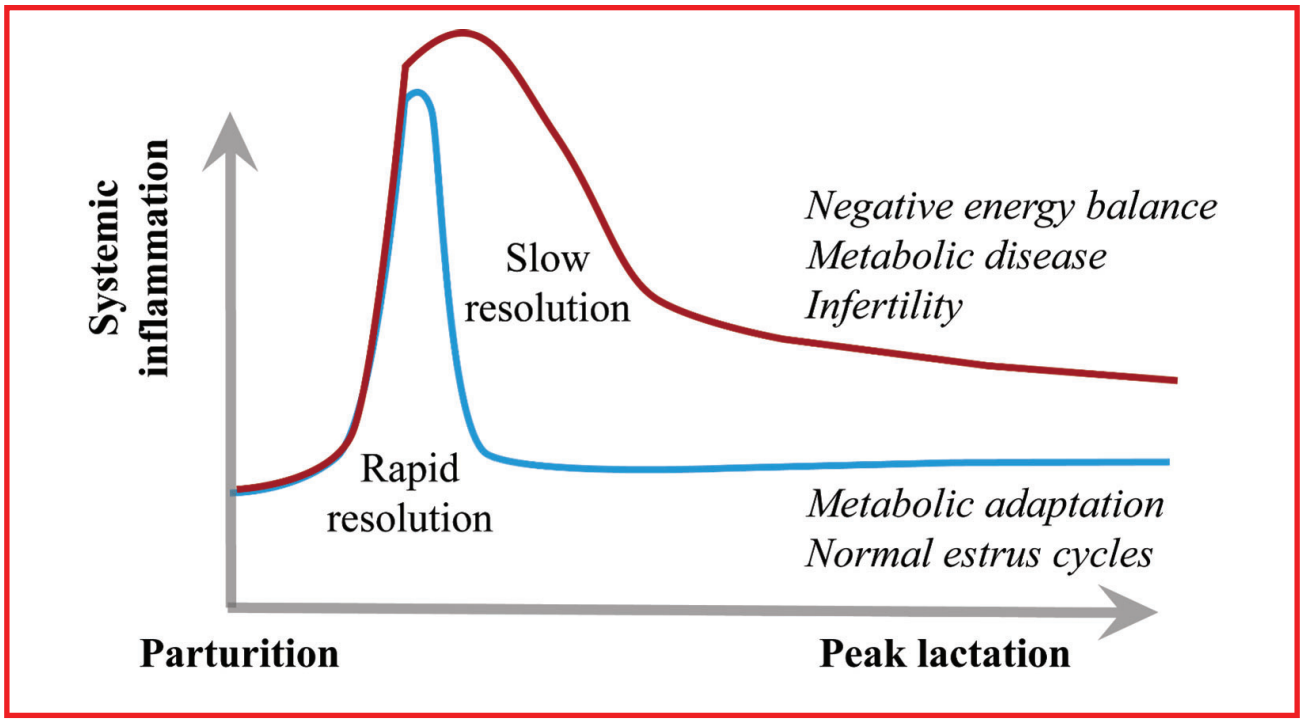

Figure 1. Hypothetical impacts of brief, rapidly resolved postpartum inflammation versus sustained inflammation. It is proposed that lack of resolution leads to impaired health and productivity rather than the inflammation per se.

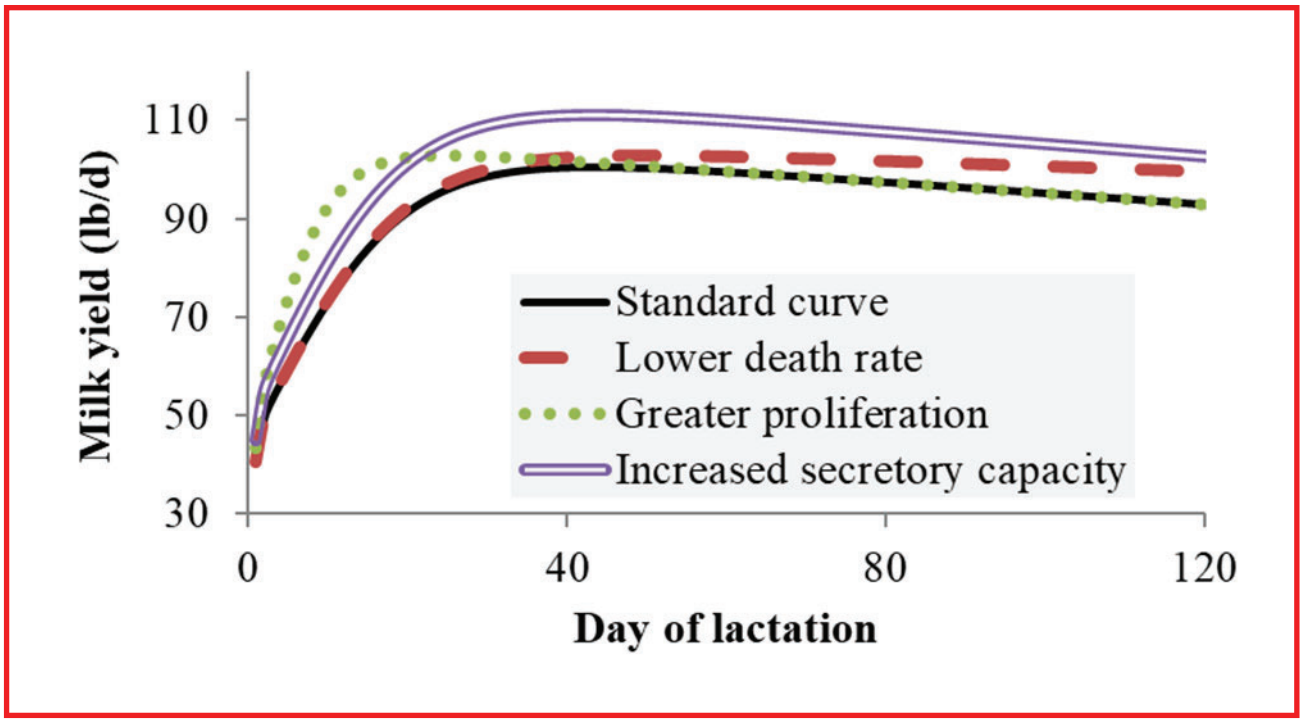

Figure 2. Exploring potential mechanisms for increased milk yield. The model of Pollott (2004) was used to predict effects of changes in mammary characteristics on the lactation curve through day 120. An average lactation curve is shown compared to curves with 50% slower cell death rate, 100% greater cell proliferation rate, or 10% greater secretory capacity per cell. Observed responses to post-calving treatment with non-steroidal anti-inflammatory drugs (Carpenter et al., 2016) and early lactation (60 days) feeding of a polyphenol supplement (Olagaray and Bradford, 2019) both altered the lactation curve in a manner consistent with predicted responses to increased secretory capacity of mammary epithelial cells.