The Central Role for Immune Signaling in Transition Cow Productivity and Health

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Introduction

Dairy producers and those who advise them are well aware of the challenges that face cows during the transition to lactation. The 2–3-week period after calving typically accounts for 40 – 50% of health problems on a dairy, and high cull rates in early lactation are a costly problem for many farms. Measures of immune function and inflammation are predictive of disease incidence in the transition period, 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). 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. Using recent data from field sampling in Michigan (Krogstad et al., 2023), we typically find that that blood haptoglobin spikes after calving, with peak concentrations on days 1 – 3 post-calving (Figure 1), and that first-lactation cows have higher haptoblogin concentrations during this period compared to older cows (Figure 2).

Beginning more than 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 blood inflammatory signals in cows through the transition period, and further showed that blood markers 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.

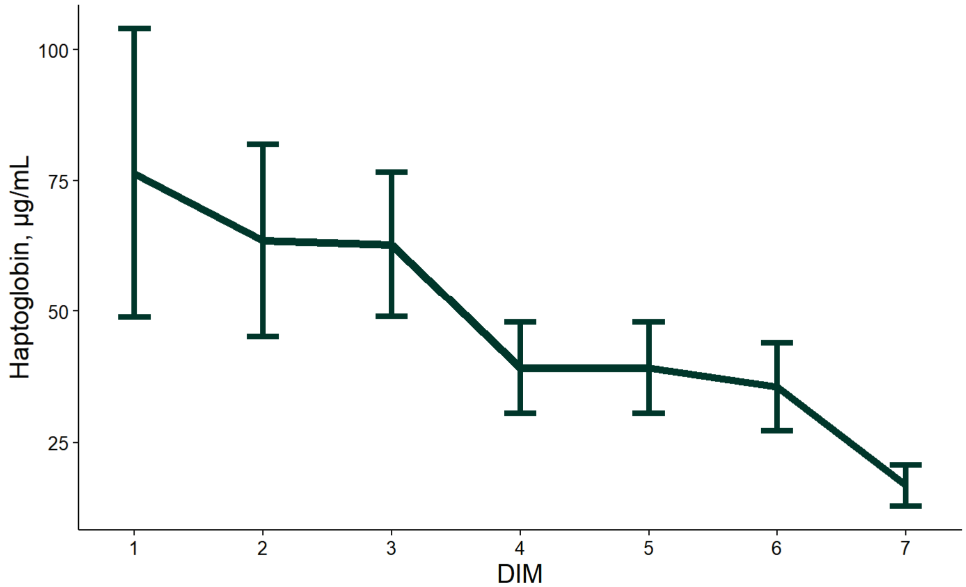

Figure 1. Concentrations of blood plasma haptoglobin, a marker of whole-body inflammation in dairy cows, across the first 7 days in milk (DIM). Data represent a single time point from each of 412 Michigan cows, clustered by DIM. The unit µg/mL is equivalent to mg/L, and can be converted to g/L by dividing by 1,000. Error bars represent the variation (standard error of the mean) at each time point, demonstrating the high variation immediately post-calving.

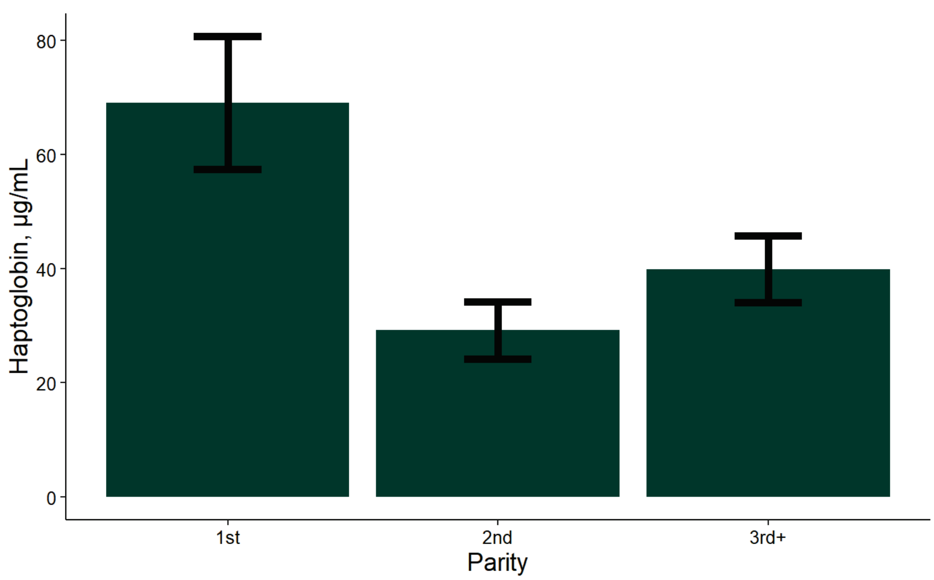

Figure 2. Concentrations of blood plasma haptoglobin, a marker of whole-body inflammation in dairy cows, during the first 7 days of lactation. Results from 412 Michigan cows were clustered by parity group, revealing that first lactation cows have significantly greater haptoglobin concentrations than cows beginning lactation 2 or greater.

More recently, groups in several countries have carried out large-scale observational studies to investigate whether elevated inflammatory biomarkers are associated with subsequent problems. 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 – 8 postpartum took longer to become pregnant (Nightingale et al., 2015). Likewise, cows with haptoglobin > 0.46 g/L in the first 17 days in milk produced 1,085 lb less milk (305-day mature equivalent) and had 28% lesser odds of becoming pregnant within the first 150 days in milk (Kerwin et al., 2023). Although there is variability across studies in cutoff values, elevated postpartum haptoglobin concentrations (greater than ~ 0.5 g/L) were consistently linked to impaired productivity, fertility, and health.

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.

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 h and 24 h 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 always being 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 markers 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%. Furthermore, in cows treated with the highest TNFα dose, 7 of 11 cows were diagnosed with at least one subclinical transition disorder, compared to just 2 of 11 in the control group. These findings demonstrate a causative role of inflammation in at least some common problems in early lactation.

One question that has not been adequately 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 3-4 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. Some recent work has shown that cows with elevated haptoglobin concentrations on both days 4 and 7 post-calving have lower blood calcium, lower milk production, and some signs of decreased liver function (Martins et al., 2021).

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. Studies going back to at least 2004 have tested various NSAIDs, doses, and timing after calving; these initial studies have been reviewed (Bradford et al., 2015). However, studies published in the last 6 years have providing increasingly detailed insights into responses to post-calving NSAID treatment.

We completed a 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 limited 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 – 9% more milk over the whole lactation compared to placebo. Barragan and colleagues (2020) 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 h before calving or within 12 h 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%). Importantly, the pre-calving treatment with meloxicam did not cause problems with calving or increase retained placenta incidence, in agreement with another study (Newby et al., 2014). Contrary to the authors' expectations, 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).

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 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., 2020). 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.

Nutritional anti-inflammatory strategies

In the United States, the NSAID strategies outlined above do not 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) have anti-inflammatory properties. Greco and colleagues (2015) used combinations of calcium salt products to offer cows diets with omega-6:omega-3 ratios of 6:1, 5:1, or 4:1 from 14-90 days in milk, while holding unsaturated fat supply relatively constant. In avoiding the first 2 weeks postpartum, this study bypassed potential impacts on the transition inflammation window, but the results were insightful nonetheless. Decreasing the omega-6:omega-3 ratio (increasing omega-3 supply) significantly increased dry matter intake as well as yields of all milk components.

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.

Assessing and monitoring herd inflammatory status

With analytical techniques currently available, there is likely little value in routine assessment of inflammatory biomarkers (e.g. haptoglobin) for making decisions on treatment of individual cows. Although many veterinary diagnostic labs do offer analyses like these, turnaround time is typically a few days when sample shipping is factored in, and by the time the result is received, the cow's status has often changed substantially. Despite the lack of a practical tool for quickly assessing inflammatory status of individual cows, there may be merit in determining herd-level inflammatory status. Many farms struggle with subpar early lactation health and performance, in some cases despite following best practices across the board. Random sampling of perhaps 20 cows in the fresh pen may provide insights into whether sub-acute inflammatory conditions may be the hidden culprit. Indeed, using a sampling approach like this (Krogstad et al., 2023) has revealed wide variation in mean (and median) plasma haptoglobin concentrations in fresh cows (1-7 days in milk; Figure 3).

Researchers at Cornell recently shared the results of the first analysis to determine herd-level alarms based on plasma haptoglobin data on cows in the first 12 days post-calving (Kerwin et al., 2022). They found that herds with > 20% of fresh cows exceeding a plasma haptoglobin concentration of 0.45 g/L had, on average, an additional 5.3% of cows with early lactation disorders (clinical ketosis and/or displaced abomasum). However, this data set was interesting in that 62 of 72 farms exceeded this threshold, suggesting that it was the herds with the low prevalence of elevated haptoglobin that stood out rather than the inverse. Further, as shown in Figure 3, our recent work with Michigan herds shows far lesser plasma haptoglobin concentrations, on average, which may reflect differences in herds, analytical methods, or both.

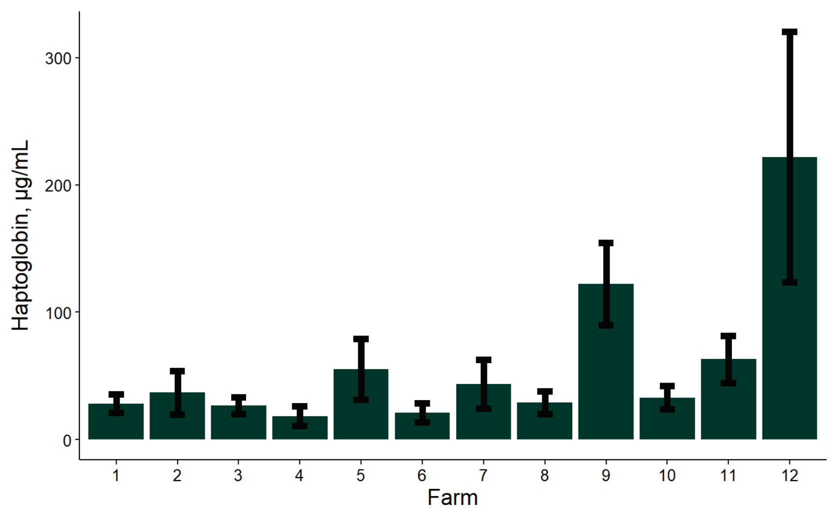

Figure 3. Concentrations of blood plasma haptoglobin, a marker of whole-body inflammation in dairy cows, across the first 7 days in milk. Results for 12 Michigan dairy farms are shown, representing 412 cows in total (n = 20 to 54 per farm).

Lab-to-lab variation in haptoglobin analysis is a frustrating reality, making it difficult to translate herd alarm levels across studies. However, if a baseline data point is established and the same laboratory is used consistently, quarterly or biannual fresh cow sampling (ideally 20+ cows) can provide a means to assess how tweaks to management or diets may be influencing cows from an inflammation standpoint. As the story on resolution of inflammation develops, it may be that the focus will shift to tracking whether cows are back to baseline by week 2 of lactation rather than worrying about week 1. Stay tuned for evolving recommendations in this space.

Take-Home Messages

- After calving, nearly all cows have subtle indicators of inflammation, even when no clinical signs are evident. This likely reflects the key role of inflammation in the calving process.
- Cows with greater concentrations of inflammation markers after calving have, on average, lower productivity, fertility, and productive life.
- Numerous studies have now shown that treatment with non-steroidal anti-inflammatory drugs around calving can have substantial impacts on the lactation curve, resulting in upwards of 10% increases in whole-lactation milk production in multiple studies.
- Feed additives are now being explored as a commercial approach to anti-inflammatory treatment, and feeds providing either omega-3 fatty acids or potent flavonoids have substantially increased peak milk yields.
- Herd monitoring for inflammatory status is a work in progress. However, very recent research has identified useful benchmarks for assessing whether inflammation is a hidden problem in a transition program overall and monitoring over time is worthy of consideration.

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