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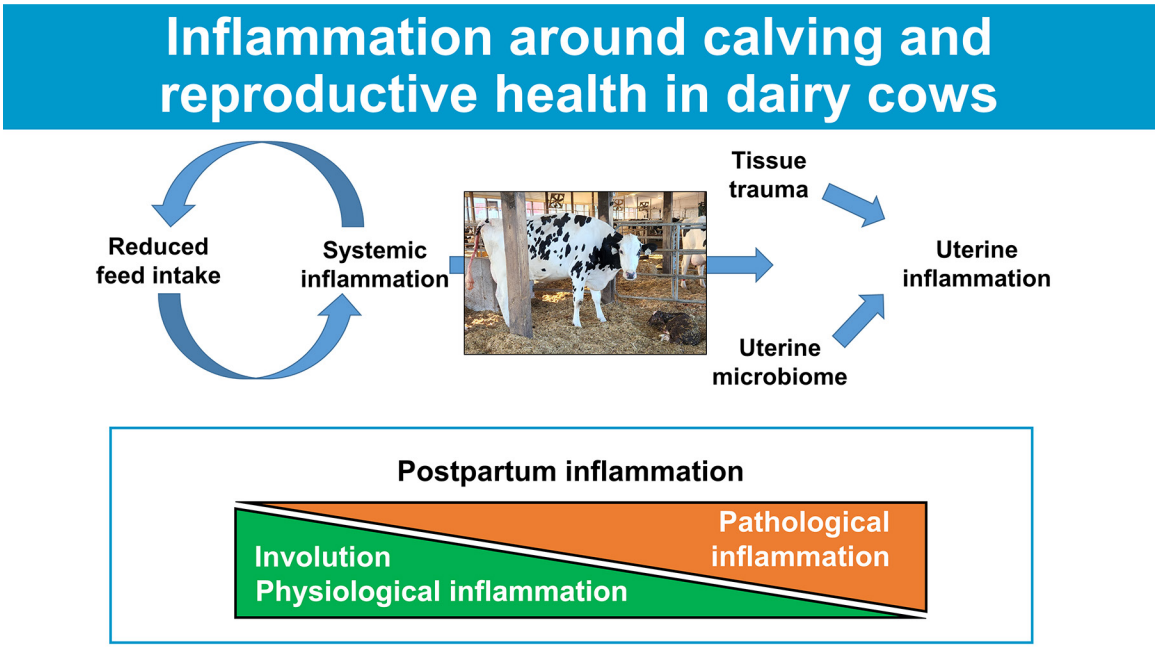
Symposium Review
Physiology and Endocrinology Symposium

Relationship of peripartum inflammation with reproductive health in dairy cows*

Stephen J. LeBlanc†

Graphical Abstract

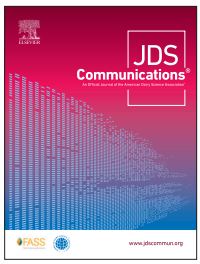


Summary

Inflammation is part of the normal process of uterine involution after calving. Inadequate immune response, trauma to the reproductive tract, and changes in the uterine microbiome soon after calving combine to cause metritis or, later, purulent vaginal discharge. In contrast, endometritis is associated with excessive or persistent uterine inflammation but generally not with bacterial infection. Uterine inflammatory disease may contribute to postpartum systemic inflammation. It is not clear what causes the chronic inflammation that characterizes endometritis but it may relate to systemic inflammation, with roots before calving.

Highlights

- The incidence and consequences of postpartum reproductive disease are tied to effective immune response and well-regulated inflammation.
- Systemic inflammation is an intriguing concept in dairy cows in the transition period, but it is not well defined.
- Metritis and purulent vaginal discharge are associated with changes in the reproductive microbiome and consequent inflammation, whereas endometritis appears to reflect persistent, dysregulated inflammation that does not seem to be caused by infection.



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Relationship of peripartum inflammation with reproductive health in dairy cows*

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Abstract: Failure of a robust but well-regulated immune response may result in reproductive tract inflammatory disease, such as metritis, purulent vaginal discharge, or endometritis. Metritis is consistently associated with reduced diversity of the uterine microbiome. Similarly, purulent vaginal discharge at 4 to 6 wk postpartum is strongly associated with bacterial infection of the uterus. Conversely, the microbiome of healthy cows and those with subclinical endometritis is generally similar, so endometritis is thought to be a consequence of dysregulation of inflammation rather than changes in uterine microbiota. There is an emerging concept that inflammation is not only a reaction to injury or disease but that it can be a consequence of or precursor to metabolic disturbances. The degree of systemic inflammation is associated with the level of trauma and bacterial contamination of the uterus or mammary gland, the degree of fat mobilization and release of nonesterified fatty acids, and perhaps leaky gut, all of which result in the release of proinflammatory cytokines. Therefore, uterine inflammation may be exacerbated by systemic inflammation, but may also contribute to heightened systemic inflammation in transition cows. However, clarity and progress are limited by a lack of validated criteria to quantify systemic inflammation and to identify its sources.

Uterine inflammation is suppressed from the time of signaling of pregnancy until parturition. The immediate postpartum period requires an immune response to inevitable uterine contamination with bacteria. Uterine disease is common in dairy cows and results from the balance between the uterine microbiome and the innate immune response and the regulation of inflammation (Lima, 2020; Sheldon et al., 2020). That balance is influenced by the metabolic status of cows adapting more or less successfully to the demands of lactation (Mezzetti et al., 2020). This paper provides a brief narrative review of current concepts of the role of inflammation in the transition period in reproductive health in dairy cows.

Systemic inflammation is a concept in biomedical science (Furman et al., 2019) that appears to have elements relevant to dairy cows in the transition period. Classically, inflammation is a response to tissue trauma or infection, producing heat, pain, swelling, or redness at the affected site. If inflammation is severe enough to produce systemic signs, there will also be fever, decreased feed intake (Brown and Bradford, 2021), and changes in social behavior (Proudfoot et al., 2014). However, new insights in human medicine in the past ~15 yr shifted this paradigm substantially. Systemic inflammation (also called sterile or metabolic inflammation) refers to chronic, low-grade inflammation that precedes and contributes to clinical disease risk (Kotas and Medzhitov, 2015). This is primarily associated with obesity in people and rodent models, in which adipose macrophages release proinflammatory cytokines [e.g., tumor necrosis factor α (TNFα)] that lead to chronic systemic inflammation and insulin resistance (Gregor and Hotamisligil, 2011). One severe form of this syndrome is nonalcoholic fatty liver disease, which bears similarities to fatty liver disease seen in dairy cows (Bobe et al., 2004). Systemic inflammation contributes to a heightened risk of type 2 diabetes and cardiovascular disease (Hotamisligil, 2017a), which do not have direct parallels in dairy cows.

There are intriguing parallels to some aspects of metabolism in transition cows that have inspired investigation of systemic inflammation in dairy cows. For example, dairy cows are in homeorrhetic (adaptive) peripheral insulin resistance, but this can be excessive or maladaptive. Most fresh cows are not obese and are in a catabolic state with substantial lipid mobilization. However, this level of oxidative stress and adipose activity might produce a state similar to metabolic inflammation in people (Mavangira and Sordillo, 2018; Bradford and Swartz, 2020; Zachut and Contreras, 2022). Short-term treatment of clinically healthy cows with nonsteroidal antiinflammatory drugs in the days after calving increased milk yield throughout lactation (Farney et al., 2013; Carpenter et al., 2018; Barragan et al., 2020). This suggests that modulation of postpartum inflammation in the absence of visible disease is beneficial and that systemic inflammation is at play in dairy cows.

The direction of the association between inflammation and feed intake in transition dairy cows is not yet clear. A small but intriguing study (Bertoni et al., 2009) of DMI in the transition period found that cows with an early and large decrease in DMI (~10% at −10 d with a further ~17% decrease at −5 d) had a substantial increase in circulating haptoglobin (**Hp**) concurrent with the onset of reduced intake. If activation of adipocytes by lipolysis and release of TNFα and IL-1β from adipose macrophages occurs because of decreased DMI, decreased intake could cause systemic inflammation (reflected in increased plasma Hp concentration). Feed restriction is used experimentally to induce "leaky gut," which could initiate inflammation (Kvidera et al., 2017), perhaps due to greater systemic exposure to LPS, but the required magnitude of restriction (≥60% reduction from ad libitum) is greater than that seen

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in Bertoni et al. (2009) or is typical before calving (Hayirli et al., 2002), even preceding clinical disease (Huzzey et al., 2007; Pérez-Báez et al., 2019). Feed restriction of 50% in late-lactation cows did not induce changes in circulating LPS binding protein, endotoxin, serum amyloid A (**SAA**), or IL-1β (Piantoni et al., 2018). We applied a 40% feed restriction for 4 d to cows 2 wk before calving (Pascottini et al., 2019). As expected, this induced substantial lipid mobilization, as evidenced by serum nonesterified fatty acid concentrations that tripled to levels similar to d −1 and 7 around calving. However, based on very similar serum concentrations of Hp and LPS binding protein during or after the feed restriction, we were not able to replicate the observations of Bertoni et al. (2009) and did not detect evidence that even a substantial reduction in feed intake could cause systemic inflammation.

Conversely, metabolic inflammation theory (Kotas and Medzhitov, 2015; Hotamisligil, 2017b) and knowledge of feed intake changes in illness (Brown and Bradford, 2021) could support the hypothesis that systemic inflammation could reduce DMI. After calving, there are numerous strong candidate causes for this scenario, reviewed by Bradford et al. (2015): calving trauma, metritis, mastitis, oxidative stress, or LPS from the rumen (Plaizier et al., 2022) or the intestinal tract (Kvidera et al., 2017). Before or after calving, social stress (e.g., due to pen changes or competition for feed access or lying space) or heat stress are additional possible triggers of systemic inflammation. Each of these is plausible, but none has compelling primary evidence in the cow as a cause of systemic inflammation in the transition period.

On average, feed intake decreases starting 4 to 7 d before calving, but healthy, high-yielding cows have little decrease, followed by a greater DMI acceleration, and absolute DMI after calving (Huzzey et al., 2007; Pérez-Báez et al., 2019). Under field conditions, between-cow variation or decreases in average prepartum intake can be magnified due to restricted feeding space and competition, social antagonism, periods of empty feed bunks or poor feed quality, heat stress, or lameness. However, despite the controlled environment of individually housed cows in research herds, there are still cows that have >20% reductions in DMI in the 7 to 10 d before calving (Hammon et al., 2006). It is an important challenge to decipher the reasons for this. If systemic inflammation is a possible cause, what could trigger inflammation in the last or second-last week before calving in cows that are neither obese nor visibly ill?

Evidence of inflammation preceding disease in dairy cows exists. Calving inherently involves inflammation, both for the process of parturition and in response to inevitable trauma to and contamination of the reproductive tract. Accordingly, healthy cows have a transient increase in circulating Hp that peaks at about 3 DIM. Cows that have metritis have 2 to 3 times greater peak serum Hp at 3 to 6 DIM, preceding diagnosis of metritis by 1 to 4 d (Huzzey et al., 2009; Dubuc et al., 2010). Similarly elevated Hp in the first week postpartum (>0.8 g/L) was also associated with 2 times greater odds of purulent vaginal discharge (**PVD**) and 1.6 times greater odds of endometritis at 35 DIM (Dubuc et al., 2010). Others have shown similar increases in markers of inflammation before metritis (Dervishi et al., 2016) or ketosis (Abuajamieh et al., 2016; Zhang et al., 2016), among other diseases. These data point to inflammation preceding disease, which is consistent with several elements of systemic inflammation (Furman et al., 2019).

The best-described mediators of acute, and perhaps systemic, inflammation are TNFα, IL-1β, and IL-6 (Holdsworth and Gan, 2015). These proteins can be measured in circulation in dairy cows, but the concentrations are low, ELISA assays are not consistently validated in the bovine (Farney et al., 2011; Sipka et al., 2022), and results may be inconsistent (Pascottini et al., 2019). Among their many effects, these proinflammatory cytokines change the synthesis and release of several acute phase proteins from the liver (Ceciliani et al., 2012). In the dairy cow, SAA, Hp, and albumin were useful markers of disease and inflammatory response in numerous studies (e.g., Huzzey al., 2009; Dubuc et al., 2010; Chandler et al., 2022; Spaans et al., 2022; Table 1).

Table 1. Putative markers of systemic inflammation[1]

In humans	In dairy cows
Acute phase protein	
C-reactive protein	Haptoglobin
Serum amyloid A	Serum amyloid A
Albumin	Albumin
	LPS binding protein
	α-1 acid glycoprotein
Cytokine	
Tumor necrosis factor α (TNFα)	TNFα
IL-1β	IL-1β
IL-6	IL-6

[1]The list is not comprehensive but represents the better-described markers used in dairy cows in studies of peripartum inflammation, reproductive disease, or experimentally induced inflammation.

Models of the acute inflammatory response can inform measurement of systemic inflammation. In experimentally induced acute inflammation in nonlactating dairy cows (i.v. LPS challenge), SAA concentrations increased in 6 to 12 h and remained elevated for 36 to 96 h (increasing with the dose of LPS from 0.01 to 1 μg/kg of BW), whereas Hp concentration increased at 36 h and was elevated until 48 to 144 h (Jacobsen et al., 2004). In dairy cows at 8 DIM, i.v. infusion of 0.625 μg/kg of BW LPS over 1 h increased SAA 3- to 4-fold at 24 h and Hp 4- to 6-fold, with the peak at 48 h; concentrations of both proteins were decreasing but still elevated at 72 h (Chandler et al., 2022). Among cows with metritis, those with lower Hp concentrations (<0.5 to 0.8 g/L) at diagnosis were more likely to cure (Machado et al., 2020). The 30% of cows with metritis that had Hp <0.5 g/L at diagnosis and were untreated in a randomized controlled trial had similar milk yield and pregnancy outcomes to cows that did not have metritis (Machado et al., 2020). Albeit among cows with clinical disease, this hints at the possibility of classifying inflammatory status into levels to which the cow can respond successfully or which exceed the cow's resilience, contribute to undesirable outcomes, and might benefit from intervention.

Although the concept fits with some of the metabolic circumstances of transition dairy cows, there are no validated criteria to diagnose systemic inflammation in cows. Some studies have attempted to classify cows or herds to an inflammatory "load" or "state" based on analysis of panels of circulating acute phase proteins in the transition period (Bossaert et al., 2012; Schmitt et al., 2021), but were of limited scope. A series of studies (summarized in Bertoni and Trevisi, 2013) identified sets of markers in plasma (e.g., acute phase proteins, bilirubin, and metabolic markers such as cholesterol and vitamin A) used to classify liver "activity" or "functionality." Although the primary studies (e.g., Trevisi et al., 2012) had small numbers of animals selected based on extremes of the indexes, the patterns of numerous markers are similar to those

Table 2. Key features of postpartum reproductive tract disease in dairy cows[1]

	Disease status		
Variable	Healthy	Metritis and PVD	Endometritis
Uterine microbiome	Diverse microbiome. Potential pathogens (e.g., *Bacteroides*, *Fusobacterium*, and *Porphorymonas* spp.) are present but in low abundance	Altered microbiome from >2 DIM. Predominance of gram-negative anaerobes and (especially for PVD) *Trueperella pyogenes*	Not associated with bacterial infection at diagnosis or with the uterine microbiome between calving and diagnosis
Physical injury	Minimal trauma at calving	Dystocia or visible physical trauma Probably greater loss or slower recovery of endometrial epithelium	Not associated with trauma
Immune response and inflammation	Fast, robust, effective, well-regulated inflammatory response in the reproductive tract Returns to baseline by ~3 wk postpartum	Impaired neutrophil function (primarily oxidative burst) precedes disease Uterine or cervical inflammation associated with pathological changes in the microbiome	Greater endometrial expression of proinflammatory genes ~2 wk postpartum (2–3 wk before diagnosis) Chronic uterine inflammation that is not associated with differences in the uterine microbiome before or at diagnosis at 4–5 wk postpartum
Response to treatment		Well-documented benefits from antibiotic therapy (systemic ceftiofur or ampicillin for metritis; local cephapirin for PVD) Little evidence of benefit from antiinflammatory therapy	Mixed evidence of benefit of antimicrobial therapy Some evidence of benefit from nonsteroidal antiinflammatory therapy

[1]Metritis refers to cows with fetid vulvar discharge with or without fever <14 d after calving. Purulent vaginal discharge (PVD) is muco-purulent or purulent discharge in the vagina at 4 to 6 wk postpartum. Endometritis is diagnosed based on >5% neutrophils in endometrial cytology at 4 to 6 wk postpartum.

seen in cows that go on to have displaced abomasum (LeBlanc et al., 2005), metritis (Huzzey et al., 2009), or endometritis (Ishikawa et al., 2004; Burke et al., 2010). Therefore, these markers may be useful candidate indicators of systemic inflammation. However, that will require a reference test. One approach would be to seek indicators of inflammation that are risk factors for subsequent disease, such as demonstrated for Hp before metritis (Huzzey et al., 2009; Dubuc et al., 2010). Another approach would be to seek markers of inflammation that identify clinically healthy cows that benefit (e.g., greater milk yield or better fertility) from receiving antiinflammatory treatment (Farney et al., 2013; Bradford et al., 2015). It remains to be seen whether systemic inflammation will be a quantifiable and actionable concept for transition dairy cows.

Systemic inflammation seems to fit as a contributor to the balance between adaptive/homeorhetic changes in support of high milk yield and maladaptation and risk of disease or reduced performance. As discussed, there are numerous plausible causes of systemic inflammation in the early postpartum period. However, to potentially explain decreased feed intake before calving that may be caused by inflammation (Bertoni et al., 2009; Trevisi et al., 2012) for at least some cows, one or more causes of systemic inflammation in the weeks before calving need to be identified. Horst et al. (2021) posited that inflammation from immune activation leads to decreased DMI and, consequently, to hypocalcemia, elevated nonesterified fatty acid concentrations, and ketosis. They suggested that this flips the direction of association dogma that these risk factors contribute to the risk of disease, reduced milk yield, or fertility; rather, if excessive, they reflect direct or indirect consequences of inflammation. This is a useful challenge to paradigms of the physiology and epidemiology of health and performance in the transition period. They assert that compromised epithelial barriers in the gut, udder, or uterus are likely sources of immune activation. They suggest that mastitis, metritis, or leaky gut lead to LPS exposure and inflammation, which is consistent with several studies (Huzzey et al., 2009; Dervishi et al., 2016; Zhang et al., 2016). However, the main gap is an explanation of what might activate the immune system and inflammation in apparently healthy cows 1 to 2 wk before calving. Some candidate causes of prepartum inflammation include obesity (which fits with systemic/metabolic inflammation in humans but accounts for a minority of cows), excessive energy intake (Khan et al., 2015; Janovick et al., 2022), or differences in the substantial inherent endocrine changes in late pregnancy (Goff and Horst, 1997).

A line of study is emerging that may help to guide investigation of the relationship between inflammation and reproductive disease. Briefly, the idea is that the balance of signals representing pathogens [pathogen-associated molecular patterns (**PAMP**)] and tissue damage [damage-associated molecular patterns (**DAMP**)] modulates immune responses. Acute inflammation may be triggered by PAMP (infection) and DAMP (trauma), but systemic inflammation is suggested to be triggered by DAMP associated with metabolic dysfunction and more chronic tissue damage (Furman et al., 2019). For postpartum reproductive disease in dairy cows, the best-described PAMP is LPS (Sheldon et al., 2019). Phospholipids are found in all plasma membranes, and oxidized phospholipids act as DAMP to signal cell damage (Zhivaki and Kagan, 2022). These authors propose that oxidized phosphocholines in particular, which are not inherently pro- or antiinflammatory, combine with PAMP to modulate innate immune threat assessment and response. Detection of PAMP without oxidized phospholipids would indicate a lesser threat and presumably a milder response, whereas detection of PAMP and oxidized phospholipids signals a greater threat and heightened response (Zhivaki and Kagan, 2022). Broadly, this aligns with elements of the pathophysiology of reproductive disease in dairy cows (Table 2). There is a shift in the microbiome of cows that develop metritis or PVD to a lower diversity and greater abundance of gram-negative anaerobic bacteria, which expose the cow locally and systemically to LPS. Additionally,

Trueperella pyogenes is an important gram-positive pathogen in uterine disease, especially PVD. A substantial part of the damage it causes appears to be attributable to its secreted toxin, pyolysin, but this has little effect on intact endometrial epithelial cells. However, if uterine stromal cells are exposed to pyolysin, as happens when the endometrial epithelium is damaged or sloughed after calving, substantial cellular damage occurs (Amos et al., 2014). Similarly, after many years without the means to reproduce PVD experimentally, a successful model uses scarification and infusion of *Trueperella* and *Escherichia coli*, as well as elevation of plasma progesterone (Piersanti et al., 2019). Tissue trauma is a risk factor for uterine disease [e.g., indicated by vulvovaginal laceration for metritis (Machado et al., 2020) or dystocia, or retained placenta for metritis or PVD (Dubuc et al., 2010)]. Additionally, local and systemic immune responses are attenuated to support pregnancy, and investigation is needed into whether and why some cows fail to upregulate inflammation successfully after calving (Hansen, 2013). Finally, although endometritis seems in many cases to reflect persistent, dysregulated inflammation without differences in the uterine microbiome (Pascottini et al., 2020), other studies show benefits to fertility with intrauterine antimicrobial treatment of endometritis (Denis-Robichaud and Dubuc, 2015).

Progress in understanding and applying the concept of systemic inflammation in transition dairy cows depends on defining and validating criteria to classify inflammation that is associated with impaired health or performance. A better understanding of the initiation and modulation of systemic and uterine inflammation will allow for improved prevention and treatment of postpartum reproductive disease.

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Notes

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