Immunological Dysfunction in Periparturient Cows—What Role Does it Play in Postpartum Infectious Diseases?

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Abstract

Periparturient cows are immunosuppressed. Critical neutrophil functions (egress and phagocytic activities) and lymphocyte functions (immunoglobulin and cytokine secretion) are all impaired during this time. Exact causes of periparturient immunosuppression are not known but tremendous fluxes in endocrine factors undoubtedly effect changes in immunological competence. Periparturient cows experience large changes in plasma concentrations of vitamins and also are adjusting to the calcium, energy and protein demands necessary for lactation. The end of gestation appears to induce a progressive suppression of immune function. There appears to be a teleological basis for suppression of antigen specific immunity in the periparturient female. Development of immunity against self and paternal antigens released into the cow as a consequence of tissue damage associated with parturition would serve little useful purpose. However, as a result of this suppression, innate immune function is also impaired (perhaps inadvertently) and opportunistic infections such as mastitis and metritis occur with increased frequency in postpartum cows.

Introduction

Periparturient cows experience a high incidence of infectious and metabolic diseases. Mastitis is one of these diseases and is typically an infectious disease characterized by inflammation of the mammary gland and abnormal lacteal secretions regardless of the cause. Mastitis is a major source of economic loss to dairy industries around the world, affecting both milk production and milk quality. Many organisms that cause bovine mastitis are opportunistic pathogens. Opportunistic bacterial infections typically occur when the integrity of native host defenses is breached and are often indicative of predisposing immunosuppression in the host animal. In the early 1980's at the National Animal Disease Center-USDA-ARS we embarked on a decidedly different approach to understand the pathogenesis of mastitis on dairy farms. Our research was driven by the observation that most clinical mastitis occurs in dairy cows in early lactation. Because bovine mastitis is caused by opportunistic pathogens we hypothesize that these cows must be immunosuppressed. This review will consider the experimental evidence supporting our hypothesis of periparturient immunosuppression.

First of all, there is an extremely high incidence of clinical mastitis in early lactation caused by opportunistic environmental pathogens (mostly coliform bacteria and streptococci other than Streptococcus agalactiae). Cows must first become infected and then develop clinical mastitis. Rates of new intramammary infections (IMI) caused by environmental pathogens are highest during the first and last 2 weeks of a 60-day, nonlactating period of dairy cows.[1-4] The rate of IMI during these periods of peak susceptibility is 2 to 12 times higher than at any other time.[1] Most coliform and environmental streptococcal infections that are established in the nonlactating period and are present at parturition result in clinical mastitis soon afterward.[1,5] The proportion of all cases of clinical coliform mastitis that develop during the first 2, 4, and 8 weeks of lactation has been reported to be 25, 45 and 60%, respectively.[6,7]

The second piece of evidence supporting the notion of immunosuppression in the pathogenesis of mastitis was that medicine traditionally teaches that opportunistic infections are associated with severe compromises of host defense mechanisms. These two points led us and others to evaluate the functional capacity of the bovine immune system around parturition. An overwhelming amount of evidence of immunological dysfunction of lymphocytes and neutrophils has been generated.[8-21] The combination of the immune system becoming progressively more compromised at the end of gestation and the poor hygiene in dry cow lots results in these cows being more readily infected in the mammary gland. As the immune system reaches its functional nadir the first week

or two after calving, these subclinical infections progress into clinical mastitis. The reduced immune function is also contributing to infectious diseases of virtually any system of the postpartum cow (gastrointestinal, respiratory and reproductive tracts all have increased disease incidence in postpartum cows).

Immunosuppression in the Pathogenesis of Mastitis

To understand the role of immunosuppression in the pathogenesis of mastitis, it is important to review the cellular immune defense mechanisms operating in the mammary gland. A key step in host defense is leukocyte recruitment into tissues following infection by microorganisms. Leukocyte trafficking through tissues is crucial for effective immune surveillance for infectious agents. Trafficking enables rapid neutrophil (innate immunity) accumulation at sites of infection or tissue injury and subsequent movement of lymphocytes (adaptive immunity) through secondary lymphoid tissues for responses against antigens presented in germinal centers.[22] The interaction of different populations of circulating leukocytes with postcapillary venule endothelial cells is essential for leukocyte emigration into tissue.[22]

Neutrophils are a homogeneous population of rather unsophisticated effector cells whose recruitment to sites of inflammation involves the coordinated function of multiple families of adhesion molecules, cytokines, and chemoattractants. A multistep-model for this process includes a transient leukocyte adhesion between the leukocyte and endothelial cells of the vessel wall mediated by members of the selectin family, followed by triggering of leukocyte activation and subsequent tight adhesion between leukocyte integrins and the intercellular adhesion molecules on endothelial cells. Selectivity in the process of leukocyte recruitment comes from the diversity of molecules capable of mediating each step. Adrenalectomy studies have shown that endocrine factors (e.g., glucocorticoids) released during stress modulate leukocyte trafficking between the blood and other immune compartments.[23]

What Causes Periparturient Immunosuppression?

Many factors contributing to the increased susceptibility to IMI and the progression to clinical disease have been fully elucidated over the past 10 years. Neutrophils can egress rapidly from the blood into the mammary gland in response to an irritant.[24] Phagocytosis and bacterial killing mechanisms of neutrophils in conjunction with humoral factors are critical defense mechanisms of the mammary gland.[25,26] Conditions that may compromise immune function include physiologic stress of lactation,[27] decreased number of circulating neutrophils capable of phagocytosis after parturition,[28,29] delayed inflammatory response in early lactation,[30-32] and impaired neutrophil microbicidal functions.[10,12,20,21] Dystocia, ketosis, and milk fever also have been associated with coliform mastitis after calving.[33,34] Investigation of immunosuppression and coliform mastitis in sows has revealed depressed neutrophil migration, ingestion of bacteria, and myeloperoxidase iodination capacity to be associated with the susceptibility to postpartum mastitis caused by Escherichia coli.[35]

Defects in lymphocyte function also contribute to the periparturient cow's increased susceptibility to mastitis. In addition to antibody production, other roles for lymphocytes in bovine mammary gland immunity include production of various hormone messengers of the immune system called cytokines. These cytokines can activate bovine macrophages and neutrophils to have enhanced activity against pathogens.[36] Suppression of various critical lymphocyte functions in periparturient cows have been reported.[11,12,15,16,18,20,37-43]

Many neuroendocrine changes develop in cows during the periparturient period. Hormonal changes during the periparturient period have been reported[44-46] and likely contribute to immunologic dysfunction. Increased plasma concentration of the endogenous opioids, β-endorphin and met-enkephalin, during the periparturient period in cows may also reduce immune function.[47] Plasma concentration of these opioids peaks at parturition and cows experiencing dystocia have significantly elevated concentrations of β-endorphin several hours postpartum compared to normal cows.

Pregnancy has been postulated to result in suppression of Th1-type immunity (i.e., cell-mediated immunity) and enhancement of Th2-type immune responses (i.e., humoral immunity). As pregnancy progresses, the ability of the immune system to produce Th1 cytokines [interferon-γ (IFN-γ and interleukin-2 (IL-2)] decreases and Th2 cytokine (IL-4, IL-5, IL-6 and IL-10) production increases.[48,49] Estrogen and progesterone play roles as suppressers of cell-mediated immune responses and enhancers of humoral responses in mice.[50] Corticosteroids are also known to suppress cell-mediated immune responses and enhance humoral responses by suppressing the production of Th1 cytokines such as IL-2 and IFN-γ.[51,52] Similar findings have been reported with cattle.[53,54] Cytokine production by bovine leukocytes is disturbed during the periparturient period in that IFN-γ and IL-2 production are dramatically reduced, suggesting suppression of Th1 immune responses.[8,16,43] It has been postulated that these changes in cytokine production might contribute to the increased incidence of disease in periparturient cows[55-57] and would certainly alter the host response to vaccination. We believe the decline in IFN-γ production is particularly damaging to phagocytic cell function. This is supported by findings that IFN-γ is capable of restoring suppressed neutrophil function.[58,59] Moreover, impairment of the

capacity of B cells from periparturient cows to secrete IgM has been reported;[20] this likely stems from impaired IFN-γ and IL-2 production.

A wide array of immunologic disturbances in cellular and humoral components of immune responses have been documented in cattle during the periparturient period and related to the marked reduction in the ability of dairy cattle to respond to invasive microorganisms.[8,10-12,17-20,42,56,57,60] Before calving, total plasma estrogen concentration increases in the cow (at least 10 times greater than during estrus).[61] Supraphysiologic concentrations of estradiol as seen at the end of gestation have been reported to suppress neutrophil function[62,63] and may be germane to immunosuppression and the high new IMI rates prior to calving.

Elevations in estrogen at the end of gestation may make immune cells more sensitive to the immunosuppressive effects of an already elevated level of progesterone, thus explaining the systemic immune suppression in the periparturient cow. How does this work? During normal pregnancy, the progesterone binding capacity of human lymphocytes is increased (perhaps as a result of increasing estrogen levels) and the concentration of progesterone in serum during pregnancy are sufficient to reduce lymphocyte functions.[64,65] This raises the possibility that hormone sensitivities of immune cells during gestation may be altered and result in functional changes in immune cells. Very high concentrations of both estrogens and progesterone are reached during the final days of gestation in cows.[61]

Many of the hormonal and metabolic changes that prepare the mammary gland for lactation take place during the 3 weeks preceding parturition. Lymphocyte and neutrophil function could be affected by prepartal increases in estrogen, prolactin, growth hormone, and/or insulin.[61,66-68] During this critical period, the dairy cow's metabolism shifts from the demands of pregnancy to include those of lactation, with increased demands for energy and protein. Negative energy and protein balances that exist during early lactation may also contribute to impaired immune function and, thus, account for a portion of the periparturient immunosuppression observed. For example, the activities of neutrophils in combating infection are complex and involve expenditure of cellular energy. The average cow has ~3,500 neutrophils per μl of blood, this translates into ~1.4 x 10^{11} neutrophils in an 1800 lb. Holstein cow. The circulating half-life of neutrophils is about 6 hours, so a cow is replacing half of her neutrophils every 6 hours from bone marrow stores. Clearly, a significant component of the dietary energy and protein consumption for maintenance is spent on replenishment of immune cells. The negative energy and protein balance of dairy cows during the periparturient period and up to peak lactation undoubtedly influence immune function. Conclusive evidence that the demands of lactation contribute to postpartum immune suppression derives from recent studies at the NADC. In studies with mastectomized cows it was found that they recover from periparturient immunosuppression within one week after calving, whereas intact lactating cows can be immunosuppressed for 2-3 weeks postpartum.[69]

What Are the Prospects for Immunomodulation to Prevent Disease?

Can we find compounds to restore immune function to the periparturient animal? Yes — but it won't be simple. It is crucial to understand that immunomodulators work best in immune-compromised hosts, hence the periparturient period is an excellent time for such compounds to be given to cows. Immunodulators must have no adverse side effects. A goal for an immune modulator for the periparturient dairy cow would be to restore innate immune function without interfering with the teleological basis of periparturient immunosuppression.

What Can We Do Until an Immune Restorative is Available?

Production of milk from mastitis-free cows is quite simple — keep them in clean, dry, stress-free environments and feed them right. Unfortunately, keeping the close-up transition cow dry and stress-free is not always done. Moreover, knowing what it means to feed her right is not well documented. Keeping cows in very clean environments is only achieved through common sense and lots of elbow grease. Minimizing stress is also common sense but also very much out of our control when it comes to environmental factors. We emphasize feeding cows optimal rations because of several indications of the influence of inadequate nutrition on immunity.

Conclusion

Giesecke[70] suggested that lactating dairy cows are unique in their response to stress, since ruminant metabolism is dependent on glycogenesis/glycogenolysis and lipogenesis/lipolysis for energy-efficient and glucose-sparing feed conversion. The lactational ability of dairy cows, combined with ruminant metabolism, may be a metabolically-demanding phenomenon unique to dairy cows. The ensuing negative energy and protein balances in early lactation may limit the immune system of cows. It is unlikely that periparturient immunosuppression is the result of a single physiological factor; more likely, it will be found that several entities act in concert with profound effects on the function of many organ systems of the dairy cow. The most clinically evident effect of periparturient stressors on dairy cows may be immunosuppression, thus explaining the high incidence of clinical mastitis. The best we can do today is to give

transition or periparturient cows the best possible hygiene conditions and appropriate diets.

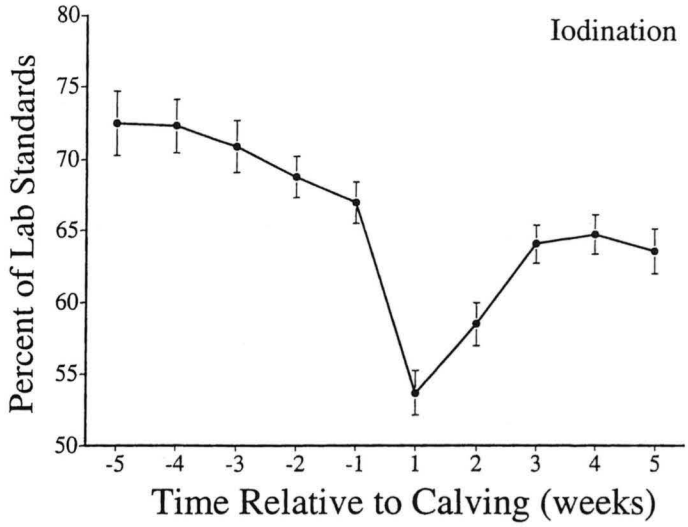

Figure 1. Suppression of neutrophil function as assessed by myeloperoxidase-catalyzed enzymatic activity. Data are from 137 Holstein dairy cows.[22]

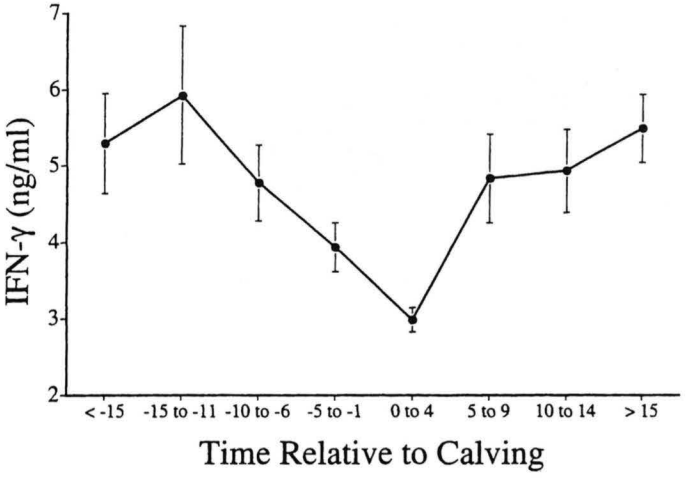

Figure 2. Suppression of lymphocyte function as assessed by in vitro induction of interferon-γ (IFN-γ) production. Data are from 6 Jersey dairy cows (Nonnecke & Kimura, unpublished).

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