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Review

# Periparturient immunosuppression and strategies to improve dairy cow health during the periparturient period

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ABSTRACT

Common health problems observed during peripartum include milk fever, mastitis, fatty liver disease, ketosis, dystocia, retained placenta, metritis, hypomagnesaemia and abomasal displacements. The increased incidence of health problems observed during the periparturient period can be partly attributed to suboptimal immune responses. Factors contributing to decreased periparturient immunity include the act of parturition itself, impaired leukocytic activity, effects of colostrogenesis and lactogenesis, and associated hypocalcemia and negative energy balance. Nutritional and other management strategies represent a relevant short-term strategy aimed at improving the health and welfare of the transitioning cow. Additionally, it is important to consider improving the health of dairy herds through the genetic selection of animals with enhanced robustness by identifying those with superior disease resistance or resilience in the face of infection. As a consequence these animals are better able to cope with the production and environmental stresses. These may provide long-term selection strategies for improving the health and welfare of the transitioning cow particularly when combined with sound management practices, allowing dairy cattle to reach their full genetic potential.



**Contents**



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## 1. Introduction

The periparturient period, also termed the transition period, is defined as the period from 3 weeks prepartum to 3 weeks postpartum, and is marked by several changes in the endocrine and immune systems in preparation for colostrogenesis, parturition and lactogenesis (Diez-Fraile et al., 2003; Drackley, 1999; Grummer, 1995; Ingvartsen and Andersen, 2000; Sordillo et al., 2009). Studies have verified that the incidence of metabolic and production-related diseases including milk fever, mastitis, fatty liver disease, ketosis, metritis, hypomagnesaemia and abomasal displacements is highest during the periparturient period and complications from dystocia and retained placenta commonly occur (Drackley, 1999; Fox, 2009; Littledike et al., 1981; Markusfeld, 1987; McArt et al., 2012; Mulligan and Doherty, 2008; Ribeiro et al., 2013; Stevenson, 2000). Several studies have attempted to identify the causes and risk factors associated with the high incidence of health problems observed during the periparturient period (Curtis et al., 1983a; Goff and Horst, 1997; Herr et al., 2011; Mallard et al., 1998; Trevisi et al., 2012). Although it is well documented that dairy cattle suffer from sub-optimal immune response during the periparturient period which predisposes them to several metabolic and production-related health problems (Goff and Horst, 1997; Lewis, 1997), our knowledge of the dynamics and pathophysiology of immunosuppression encountered during this period continues to evolve. Previously, selection for production traits with little or no emphasis on health and fitness traits coincided with a higher incidence of disease in dairy cattle, including mastitis which is unfavourably genetically correlated with production traits (Oltenacu and Algers, 2005; Oltenacu and Broom, 2010). This increase in disease incidence is especially evident during the periparturient period when a temporary impairment in immune function (immunosuppression) occurs (Goff and Horst, 1997; Kimura et al., 2006). The combined effects of multiple stressors incurred as a result of nutritional deficiencies, parturition, transition to the milking herd and herd management procedures during the periparturient period can both increase and prolong the magnitude of immunosuppression, further increasing susceptibility to diseases and negatively impacting on the animal's ability to overcome disease and recover. One of the challenges to our understanding of the effects involved is that the transition period includes a myriad of hormonal and metabolic changes, such that it can be difficult mechanistically to identify cause and effect. In this review we aim to explore the causes of periparturient immunosuppression and propose short- and long-term strategies aimed at improving dairy cow health and welfare during this critical period.

## 2. Transient causes of immunosuppression

### 2.1. Parturition

The act of parturition is a 'stressful event' that induces the production of glucocorticoids accompanied by signaling and coordination from the hypothalamus, pituitary gland and adrenal glands. Studies have suggested that cortisol is the most dominant glucocorticoid in the cow (Gwazdauskas et al., 1972; Venkataseshu and Estergreen, 1970). Stress responses in the body due to physiological or pathological factors stimulate the hypothalamus-pituitary-adrenal axis in a similar manner (Diez-Fraile et al., 2003). Effector molecules produced during stress episodes include norepinephrine, epinephrine and glucocorticoids. Circulating norepinephrine and epinephrine stimulates the production of anti-inflammatory cytokines such as transforming growth factor-β (TGF-β) and interleukin -10 (IL-10) which in turn inhibits the production of pro-inflammatory cytokines such as interferon γ (IFN-γ), tissue necrosis factor α (TNF-α) and interleukin-12 (IL-12). Inhibition of pro-inflammatory cytokine production causes immunosuppression, selectively suppressing cellular immunity and promoting antibody-mediated immunity (Elenkov and Chrousos, 2002; Kasprowicz et al., 2000; Madden et al., 1995). Down-regulation of glucocorticoid receptor expression on leukocytes in the periparturient cows has been associated with increased cortisol concentrations (Preisler et al., 2000a, b). Circulating cortisol levels influence immune responsiveness by directly inhibiting T-cell proliferation, T-cell development, modifying the action of complement molecules and interfering with immunoglobulin function. Changes in circulating cortisol levels around parturition are thought to play a critical role in development of immunosuppression, increasing disease susceptibility (Lewis, 1997; Mallard et al., 2009). Studies have also demonstrated that circulating glucocorticoids induce down regulation of L-selectin and CD18 expression on the surface of neutrophils, reducing surveillance activity and, as a result, reducing immune response capacity (Burton et al., 2000; Burton et al., 1995; Mallard et al., 2009; Preisler et al., 2000b).

### 2.2. Impaired leukocytic activity

Impaired neutrophil and lymphocyte activity observed in cows during the periparturient period is thought to be primarily due to the effects of glucocorticoids (Preisler et al., 2000a; Preisler et al., 2000b). The consequences of impaired function and killing activity of neutrophils on disease incidence have been reviewed elsewhere (Burton and Erskine, 2003; Lewis, 1997) (Nauseef and Borregaard, 2014). Neutrophils function primarily to phagocytose and destroy pathogens. Prior to phagocytosis, neutrophils must sense and migrate to the sites of infection via interactions with adhesion molecules and chemoattractant molecules expressed on endothelial linings. Once at the site, neutrophils not only phagocytize foreign bodies but are also able to sense and acquire fragments from damaged and dead cells (Whale et al., 2006; Whale and Griebel, 2009). Impaired neutrophilic activity is characterized by reduced activation, chemotaxis, adherence, pathogen ingestion, respiratory burst and release of lytic enzymes (Rinaldi et al., 2008; Sordillo and Aitken, 2009). Several studies have reported that neutrophil function is impaired within the transitioning period. Reduced chemotactic activity of neutrophils isolated from periparturient cows has been demonstrated in vitro (Kimura et al., 2002). Findings revealed that neutrophils from cows with retained placentas have reduced chemotactic responses to cotyledon material when compared to neutrophils from cows which expelled their placenta in the normal time frame (Cai et al., 1994; Gunnink, 1984a, 1984b). Changes in neutrophil gene expression during the periparturient period result in altered expression of important proteins involved in their structural integrity and functionality (Madsen et al., 2002; Meglia et al., 2001; Tan et al., 2012). Such findings suggest that impaired neutrophil activity contributes significantly to immunosuppression in the dairy cow.

Mononuclear leukocytes also protect the body against invading pathogens. Macrophages phagocytize, engulf and destroy pathogens but also digest short-lived neutrophils at sites of infection once they have completed their phagocytic duties, thereby playing an important role in innate immunity. In contrast, lymphocytes play a critical role in cell and antibody-mediated adaptive immune responses. Altered populations and function of mononuclear leukocytes have been observed in cows during the periparturient period. Reduced numbers of circulating monocytes, and various lymphocyte subsets, were reported during the prepartum period compared with the post-partum period (Harp et al., 1991; Kimura et al., 1999a; Nagahata et al., 1992; Park et al., 1992). A decrease in the serum concentration of certain immunoglobulin classes has also been demonstrated during the periparturient period. Herr et al. (2011) observed physiological evidence of decreased IgM and IgG1 serum concentrations in the periparturient period. It is well documented that significant amounts of IgG1 of serum origin are transported into mammary secretions during colostrogenesis (Hurley and Theil, 2011). The ability of bovine leukocytes to secrete pro-inflammatory mediators during the periparturient period was found to be influenced by certain vitamins. For example, lymphocytic activity is inhibited by the surge of vitamin D components [1α, 25-dihydroxyvitamnin D3]