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Transition stress and its amelioration in lactating animals

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Abstract
The most crucial time period is known as the transition phase, which lasts from three weeks prior to calving to three weeks post, where animals are challenged to undergo many biochemical, metabolic, and endocrine adjustments. Within a few weeks, cows are submitted to many challenges (physiological, nutritional, psychological, and management) that require prompt and effective adaptive responses, or else they will enter transition stress. Transition stress in the form of increased oxidative stress. Around parturition, cows are immunosuppressed and their immune systems are dysregulated. Systemic inflammation and generation of negative energy balance (NEBAL) and ketone bodies through lipolysis play a significant role in early lactation and affect many liver functions (fatty liver disease), which is directly and indirectly associated with the impairment of cow performance i.e., reduced feed intake, milk yield, fertility, and health disorders like ketosis, milk fever, mastitis, metritis, LDA, retained placenta and udder oedema. Growth hormone coordinates nutrient partitioning in dairy cattle by increasing glucose synthesis in the liver and mobilizing lipids from adipose tissue. Through proper assessment and nutrient fulfilment, the transition stage can be managed in dairy cattle. Feeding higher energy diets supplemented with antioxidants and trace minerals and vitamins in the transition diets of high yielders can help to overcome the transition stress. In conclusion, transitional stress can have negative effects on the immune function of lactating animals, leading to increased susceptibility to diseases and infections. However, the use of dietary supplements and management practices can help ameliorate these effects, improving the health and productivity of lactating animals.

Keywords: Transition period, transition stress, immunity

Introduction
Transition period refers to the period from 3 weeks before calving extending up to 3 weeks after calving and consider the most critical period in dairy animals, where animals are challenged to undergo many biochemical, metabolic, and endocrine adjustments (Grummer, 1995) [1]. The transition period is characterized by dynamic changes in the hormonal profile, loss of appetite, negative energy balance, nutrient and vitamin deficiencies, compromised immunity, and oxidative stress. These factors can disrupt at the cellular, tissue, and molecular levels, thus enhancing the occurrence of the diseases that commonly affect cows during the transition period, including postpartum paraplegia, slow uterine involution, retention of placenta, ketosis, mastitis, fatty liver disease, and abomasum displacement (Sobiech *et al.*, 2015) [2]. Most infectious diseases and metabolic disorders occur during this time. Immunosuppression during the periparturient period leads to increased susceptibility to mastitis. Indeed, the incidence of environmental mastitis is greatest around parturition. Thus, the occurrence of health problems is centered disproportionately on this relatively short period, which certainly contributes to making this an “interesting” time for dairy producers.

Transitional stress can have a negative impact on the immune system of lactating animals, making them more susceptible to diseases and infections. Understanding the relationship between transition stress and immunity is crucial for developing effective strategies to mitigate the negative impacts. This introduction provides an overview of transition stress and immunity in lactating animals and explores potential approaches for ameliorating the stress. Transition stress refers to the physiological, metabolic, and environmental challenges that lactating animals experience during the transition period, which includes the periparturient and early lactation stages. This period is marked by a series of complex hormonal, metabolic, and immunological adaptations as the animal transition from late pregnancy to milk production. However, these adaptations can disrupt the delicate balance of the immune system, making the animals more susceptible to infections, metabolic disorders, and other health issues.

The immune system plays a vital role in defending lactating animals against pathogens and maintaining their overall health. However, the stressors associated with the transition period can have profound effects on immune function. Research has shown that transition stress can lead to immune suppression, characterized by reduced immune cell function, impaired antibody production, and altered cytokine profiles. These immunological changes can compromise the animal's ability to mount an effective immune response, increasing its susceptibility to infections and diseases.

To ameliorate transition stress and support immune function in lactating animals, several strategies can be implemented. These include optimizing nutrition to meet the increased demands during the transition period, managing body condition scores to ensure adequate energy reserves, providing comfortable housing and minimizing social stress, and implementing effective disease prevention and monitoring programs. Furthermore, collaborative efforts between veterinarians, nutritionists, and other professionals can help develop tailored management practices to alleviate transition stress and enhance immune function.

Physiological Changes During Transition: immune and metabolic variations

Cows face a significant challenge due to a sudden surge in nutritional requirements for milk production, surpassing the intake and nutrient supply. The demand for nutrients to support milk production leads to the use of body reserves, causing an inevitable state of negative energy balance (Ingvartsen, 2006) [3]. This situation is compounded by additional stressors or management practices that further decrease dry matter intake (DMI) (Rhoads *et al*., 2011) [4]. The physiological conditions arising from inadequate energy supply make dairy cows susceptible to metabolic and microbial ailments like milk fever, endometritis, ketosis, displaced abomasum, and retained placenta. Inflammation and disrupted immune responses have been suggested as crucial factors in the development of metabolic issues during the transition period. Research indicates that inflammatory agents directly trigger metabolic imbalances (Trevisi *et al*., 2010) [5]. Moreover, many metabolic hormones and their receptors undergo changes around calving, which are necessary for successful lactation initiation and adaptation to increased milk production demands. However, these changes can also result in variations in immune and metabolic functions that require careful management to ensure cow health and productivity.

Immune Variations

a) **Immune Suppression:** The transition period is characterized by immune suppression, where the cow's immune system is temporarily compromised. This immune suppression is partly driven by hormonal changes and metabolic adaptations associated with parturition and lactogenesis. Reduced immune cell function, impaired antibody production, and altered cytokine profiles contribute to decreased immune responses and increased susceptibility to infections.
b) **Inflammatory Responses**: Despite immune suppression, cows experience localized and systemic inflammatory responses during the transition period. These inflammatory responses are triggered by tissue damage during calving and the release of pro-inflammatory cytokines. While inflammation is a necessary part of the healing process, excessive or prolonged inflammation can have negative effects on cow health and milk production.

Metabolic Variations

a) **Negative Energy Balance (NEB):** One of the most significant metabolic changes during the transition period is the onset of NEB. High energy demands for fetal growth and colostrum/milk production exceed the cow's energy intake, resulting in a temporary energy deficit. NEB leads to the mobilization of body fat stores, resulting in increased circulating non-esterified fatty acids (NEFAs) and ketone bodies. Prolonged or severe NEB can lead to metabolic disorders such as ketosis and fatty liver.
b) **Glucose Homeostasis:** The transition period is characterized by altered glucose metabolism. Insulin resistance develops as a result of hormonal changes and metabolic adaptations, reducing the cow's ability to utilize glucose effectively. The liver's capacity to produce glucose through gluconeogenesis increases to meet the energy demands. However, the balance between glucose production and utilization is often disrupted, leading to fluctuations in blood glucose levels.
c) **Mineral and Vitamin Imbalances**: The transition period can also result in mineral and vitamin imbalances. The demand for minerals and vitamins increases significantly during late pregnancy and early lactation. Inadequate intake or inefficient absorption can lead to deficiencies or imbalances, negatively impacting immune function, reproductive health, and overall cow performance.

Energy homeorhesis during transition stress

Energy homeorhesis refers to the coordinated metabolic adaptations that occur in an animal to maintain energy balance and meet the energy demands during periods of stress or metabolic challenges. The transition period in dairy cows is a time of significant metabolic stress, characterized by hormonal, physiological, and environmental changes. These stressors can disrupt energy homeostasis and lead to negative energy balance (NEB), which has profound effects on cow health and productivity.

During transition stress, cows experience an increased energy demand due to the onset of lactation and the need to support milk production. However, the cow's ability to consume and utilize energy is often compromised, leading to a state of NEB. NEB occurs when energy demands exceed energy intake, resulting in the mobilization of body fat stores to meet the energy deficit.

Hormonal changes associated with transition stress

It plays a critical role in regulating energy homeorhesis. Several key hormones, such as insulin, glucagon, cortisol, and growth hormone, interact to modulate energy metabolism and ensure the availability of glucose and fatty acids for energy production.

Insulin: Produced by the pancreas, facilitates the uptake of glucose by tissues and promotes its utilization for energy. However, during transition stress, insulin sensitivity is reduced, leading to impaired glucose uptake and utilization. This insulin resistance is believed to be influenced by hormonal changes, inflammatory responses, and alterations in adipose tissue metabolism.

Glucagon: Pancreatic hormone, released in response to low blood glucose levels and promotes glucose production through gluconeogenesis in the liver. Glucagon plays a crucial role in maintaining blood glucose levels during NEB by stimulating the breakdown of stored glycogen and promoting the synthesis of new glucose molecules.

Cortisol: Stress hormone produced by the adrenal glands, is also involved in energy homeorhesis during transition stress. Cortisol mobilizes energy stores by promoting the breakdown of muscle protein, increasing gluconeogenesis, and stimulating lipolysis. However, chronically elevated cortisol levels can have detrimental effects on cow health, including immune suppression and increased susceptibility to metabolic disorders.

Growth hormone (GH): Hormone that influences energy homeorhesis during transition stress. GH promotes lipolysis and the release of fatty acids from adipose tissue, providing an alternative fuel source to glucose during periods of NEB. GH also affects insulin sensitivity and metabolism in various tissues.
The disruptions in energy homeorhesis during transition stress can have significant consequences for cow health and performance. Prolonged NEB and imbalances in energy metabolism can lead to metabolic disorders such as ketosis, fatty liver, and displaced abomasum. These conditions not only impact milk production but also increase the risk of other health issues and reproductive problems. Managing energy homeorhesis during transition stress is crucial for minimizing the negative effects on cow health. Proper nutrition, including balanced diets that meet the increased energy demands, can help alleviate NEB and support energy homeostasis. Monitoring cow health, body condition score, and metabolic parameters can aid in early detection and intervention to prevent metabolic disorders. Additionally, stress management, comfortable housing, and disease prevention measures contribute to reducing the overall stress burden on cows and promoting energy balance.
The transition period for cows involves significant stress factors impacting their overall health and energy balance.

Key elements during this phase include:
1. Decreased immune function (Goff & Horst, 1997) [6].
2. Negative energy balance (NEB), leading to the use of fat and muscle tissue for energy (Drackley, 1999) [7].
3. Hypocalcemia, caused by a delay in calcium availability for sudden high demands in milk synthesis (Martinez *et al*., 2012) [8].
4. Systemic inflammation post-calving, often occurring even without evident signs of infections (Bertoni & Trevisi, 2013) [9].
5. Oxidative stress due to an imbalance in antioxidants alongside an increase in pro-oxidant molecules (Celi, 2018) [10].

These critical aspects during the transition period significantly impact cows' overall stress levels and their ability to maintain energy equilibrium.

Metabolic disorders associated with energy nutrition and challenges for the transition cow

Ketosis and fatty liver syndrome

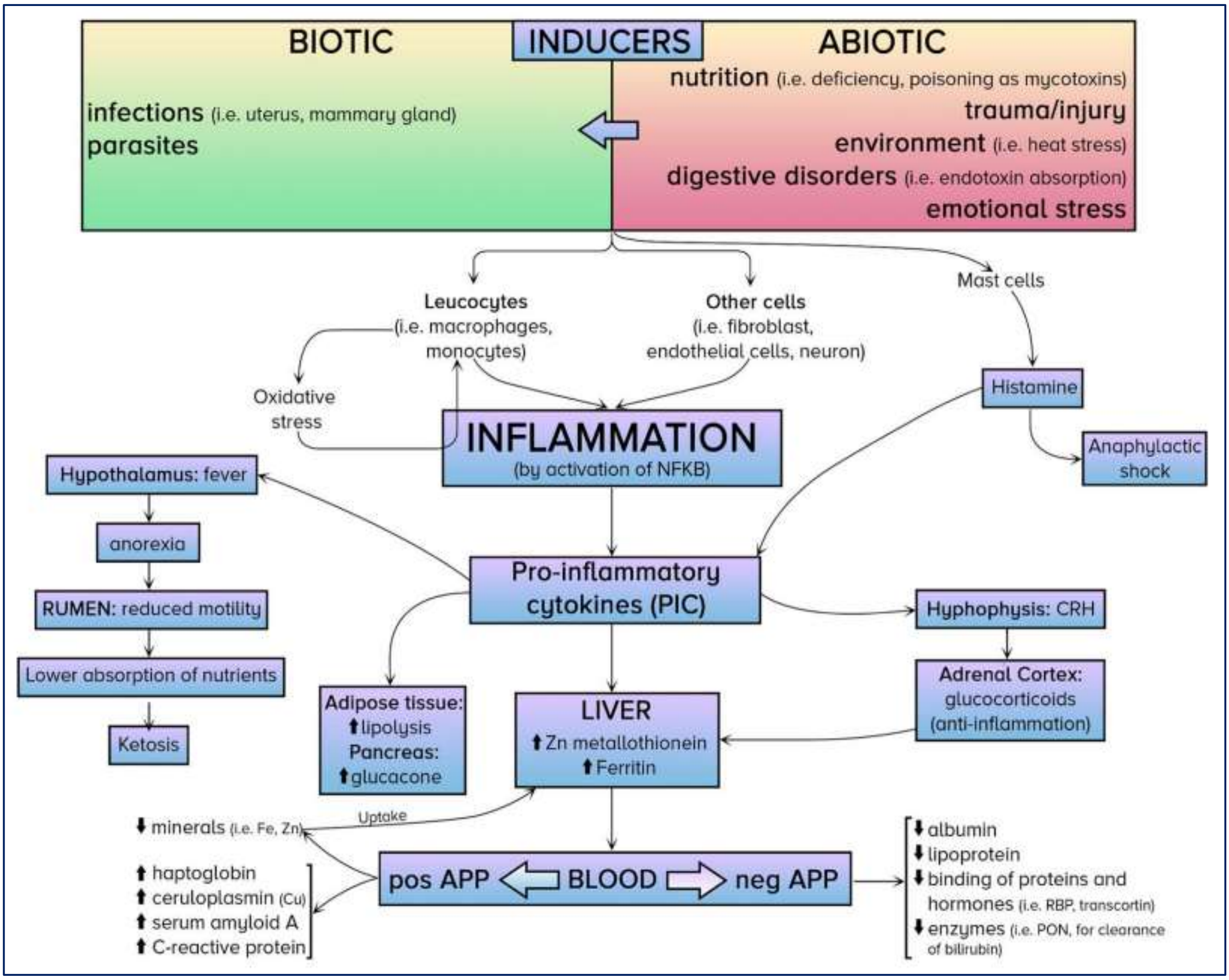
Ketosis, a condition common in early lactation in cows, results from the unbalanced utilization of body fat, leading to low blood glucose levels (hypoglycemia) and increased ketone levels (hyperketonemia). Reduced blood glucose prompts a decline in plasma insulin and the release of stored fat as non-esterified fatty acids (NEFA). The complete breakdown of NEFA generates acetyl coenzyme A, which is usually used for energy production via the Krebs cycle. However, excess acetyl Co A can lead to the production of ketones (acetoacetic acid, acetone, and β-hydroxybutyrate or BHB). Elevated ketone levels result in clinical ketosis. It is estimated that around half of all dairy cows experience a brief phase of subclinical ketosis during the first month of lactation. To address this issue, management strategies focusing on optimizing dry matter intake (DMI), increasing dietary energy density without compromising rumen function, and maintaining a body condition score of 3.5 on a scale of 1 to 5 at calving are recommended (Macdonald and Roche, 2004) [11].

Displaced abomasum

Left-displaced abomasum (LDA) commonly affects high-yielding dairy cows after calving (Geishauser, 1995) [12]. In postpartum cows, the abomasum can shift to the left without displaying clear clinical symptoms (Van Wimden *et al*., 2002) [13]. The early postpartum phase is deemed the main risk period for this condition due to factors like low calcium levels, metritis, negative energy balance, and nutritional issues playing a significant role in LDA's development (Shaver, 1997) [14]. The impact of compromised immune responses in LDA is not fully understood. Approximately 50% of LDA cases coincide with negative energy balance (NEB) (Heuer, 2000) [15].

Immune system during the transition period

The immune system, composed of lymphoid organs, cells, and signaling molecules like cytokines, works as an integrated network designed to detect, combat, and remove various intruders, whether biotic or abiotic, that breach the body's protective barriers (Bertoni *et al*., 2015) [16]. During the transition period, cows are more likely to encounter situations that stress the immune system, leading to the activation of the innate immune response (Trevisi, *et al*., 2018) [17].



These occurrences stem from both living (biotic) factors like pathogens, viruses, and parasites, as well as non-living (abiotic) factors such as climate, nutrition, social aspects, and metabolism (Trevisi *et al*., 2016) [18]. There are various non-infectious factors that are highly pertinent during this critical physiological period, including psychological stresses like isolation, overcrowding, and grouping (Loor *et al*., 2013) [19], nutritional considerations (Bertoni *et al*., 2016) [20], oxidative stress (Sordillo & Mavangira, 2014) [21], and environmental conditions. Notably, the issue of weakened immunity during the transition period deserves specific attention. Certain immune system functions, such as neutrophil phagocytosis, experience a decline before calving (Lacetera *et al*., 2005) [22], the ability of lymphocytes to respond to mitogens and to produce antibodies (Mallard *et al*., 1998) [23], The process of DNA synthesis in peripheral blood mononuclear cells and the levels of essential components in the plasma, such as immunoglobulins, IFNγ, complement, and lysozyme, have been examined in several studies. Changes in immune response have been linked to various health issues, including the resurgence of current intra-mammary infections or the onset of new mammary infections, postpartum uterine problems like retained placenta or metritis (Sheldon *et al*., 2008) [24], as well as with obesity.

Nutritional Strategies to manage transitional stress
Oxidative stress in the transition period is thought to heighten the risk of diseases. It happens when reactive oxygen radicals overwhelm the body's antioxidant defense mechanisms. Various essential trace minerals and nutrients are vital for an efficient antioxidant defense system.

Antioxidants: Antioxidants including vitamin A and selenium are important in the weight-reduction plan of transition animal due to their capability to neutralize ROS, thereby preventing inflammation.

Selenium and Vitamin E
Selenium is a vital micronutrient crucial for various metabolic processes, serving as a co-factor for numerous enzymes and seleno-proteins like glutathione peroxidase. Both selenium and vitamin E work together to support the cow's immune system, enhancing the effectiveness of neutrophils in combatting invading bacteria. Cows lacking selenium displayed higher concentrations of bacteria in their milk compared to those supplemented with selenium. Vitamin E levels in the bloodstream decreased during the transition period due to its utilization in colostrum production, contributing to an imbalance in antioxidant status linked with disorders in transition cows. Several studies have demonstrated that supplementing selenium-deficient diets in cows reduced the incidence of retained placentas in dairy cows.

Copper
Copper plays a crucial role in the antioxidant system as it is a component of the copper-zinc superoxide dismutase enzyme. This enzyme aids in transforming superoxide radicals into

hydrogen peroxide within the cell. Introducing copper into the diet influences both phagocytic and specific immune functions.

Zinc

Zinc, a metal-binding protein, functions to eliminate hydroxide radicals. Its presence can influence immune function due to its critical involvement in cell replication and proliferation. Studies indicate that severe zinc deficiency in calves can negatively affect their immune system. While plasma zinc levels typically drop in newborn farm cows, they generally return to normal within three days.

Chromium

Chromium forms part of the Glucose Tolerance Factor (GTF). The recommended daily dietary intake of chromium for dairy cattle is established at 0.5 mg/kg DM (FDA, 2009) [25]. Chromium enhances insulin activity, aiding the interaction between insulin and the insulin receptor in target tissues. There is a belief that chromium indirectly impacts the immune system by counteracting the effects of cortisol (Kafilzadeh *et al*., 2012) [26]. It assists in insulin metabolism and the utilization of glucose. Adding chromium to feed decreases the occurrence of ketosis.

Fat supplementation in transition diet

Conjugated linoleic acids (CLA)

Feeding these isomers in a rumen-protected form to transition dairy cows reduces negative energy balance and NEFA and BHB levels. CLA supplementation increases DMI and some of the negative acute phase proteins such as albumin and cholesterol (Esposito *et al*., 2013) [27]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are recognized for their ability to reduce arachidonic acid levels within cell membranes. These fatty acids operate at a molecular level to diminish the production of typical inflammatory cytokines like tumor necrosis factor (TNF) and interleukin-6 (IL6. They also decrease the presence of adhesion molecules involved in the inflammatory interaction between leukocytes and endothelial cells (Calder, 2006) [28]. Omega-3 polyunsaturated fatty acids (Ŵ-3 PUFA) may adjust the expression of genes associated with inflammation by suppressing the activity of certain transcription factors and inflammatory cytokines. It's suggested that they directly influence pathways related to inflammatory gene expression via Toll-like Receptor 4. More recently, diets rich in Ŵ-3 fatty acids have been shown to regulate immune responses, such as the febrile response induced by LPS (lipopolysaccharides) (Farran *et al*., 2008) [29]. They also affect the cell-mediated immune response through the influence of fish oil.

Methyl donors

The primary focus on choline's potential applications in the nutritional aspects of transition cow diets has largely revolved around its function in lipid metabolism. This is because the liver requires phosphatidylcholine for the creation and release of VLDL (very-low-density lipoprotein). Both of these amino acids also show promise in aiding the liver's mitochondrial B-oxidation of fatty acids (in the biosynthesis of carnitine) and in the export of triglycerides as VLDL (in the biosynthesis of apolipoprotein B100). Speculation about methionine's potential role in bovine ketosis has persisted for over 30 years. Reports suggest that increasing methionine supply, whether through rumen-protected methionine or its analog [2-hydroxy-4-(methylthio)butanoic acid], from before parturition through early lactation, generally leads to increased milk production during the early lactation phase. Consequently, the specific contributions of methionine and lysine in influencing hepatic lipid and glucose metabolism are currently conjectural and lack concrete evidence.

Conclusion

Throughout the transition phase of dairy cows, numerous significant changes take place that impact the inherent immune system. The intricate nature of this immunity makes it challenging to comprehend the source of its decline, particularly when specific immune areas like the uterus or mammary gland are involved. Nevertheless, certain aspects of the innate immune system can serve as indicators, signaling the surpassing of critical thresholds or indicating the severity of physiological impairment. Certain biomarkers linked to the liver's inflammatory response (particularly negAPPs) and observed within the initial month of lactation, are associated with adverse and enduring effects witnessed in dairy cows, spanning their health, well-being, fertility, and longevity. The real target remains the discovery of early biomarkers in late pregnancy which can be used to identify cows that will have a risky transition period. Inflammatory immunological responses are the foundation for production disorders in transition dairy cows that result in financial losses. Nutritional measures that lessen susceptibility to production illnesses are necessary. The relationship between immunity and nutrition is still only partially understood. To clarify the immunological responses of periportal diseases, reliable instruments to evaluate the immune condition of the cow must be created. It is necessary to use integrative methods at the molecular, cellular, and animal levels to understand the intricate relationships between immunological and metabolic processes that underlie periparturient disorders.

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