Managing Calf Health and Performance in utero

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- **Take Home Messages**
  - Late gestation interventions on the cow can alter the performance and health of the developing calf after birth.
  - Supplementation of the dam with specific nutrients such as choline may be required for optimal growth and immune function of the calf.
  - Disease outcomes, such as fever, in late gestation of the cow may alter the calf’s responses to similar stimuli after birth.
  - Environmental challenges, such as heat stress, program deficits in calf growth and health, and those impacts are transgenerational.

- **Introduction**

There is now little argument about the importance of good calf nutrition and management to ultimate productivity in the milking herd, especially in the early weeks before weaning. This knowledge has resulted in significant improvements in calf feeding and health monitoring because those are viewed as an investment that yields strong returns in productivity and health down the line. One example is that most farms have a specific protocol to ensure that newborn calves receive sufficient volumes of high-quality colostrum within the first 24 hours of life, with the initial feeding within 4 hours of birth. Because calves are born with a naïve and immature immune system, colostrum intake is critical to calf health and survival, and ultimately productivity. Recognition that calf lean mass accumulation progresses at a maximal rate early in life led to re-examination of feeding regimens to accelerate growth, with significant improvements in productivity at maturity relative to traditional rates of milk replacer and milk feeding. Of course, appropriate housing with particular attention to ventilation is essential to reduce disease and avoid cold stress. A well-designed vaccination protocol also should be in place to improve resistance to disease as calves transition through weaning.

While the aforementioned improvements to nutrition and management of calves have resulted in greater performance as those animals move through early life and as they enter the production string, less attention has been paid to factors that alter in utero calf development. Emerging evidence suggests that significant influences of in utero insults to the calf as it develops are associated with limits to performance and health after birth that might persist into adulthood. Because developmental trajectories are particularly plastic in the developing fetus, the concept of fetal programming or epigenetic imprinting has been promoted as a mechanism whereby nutrient or environmental factors can affect the fetus and influence that animal for life (Reynolds et al., 2019). More importantly, these epigenetic effects can be transmitted to the offspring of the affected animal and thus impact future generations. Below we consider some examples of nutrient deficiencies, pathogen exposure and environmental insult that may alter fetal development and, if ignored, may negatively impact performance and health of the calf for life.
In utero Nutritional Deficits

Poor nutrition of the dam can lead to energy or protein related limitations to fetal growth, and severe deficiencies will reduce birthweight and negatively impact growth. Indeed, stunted calves may never catch up with normal herd mates. In contrast to systems in which cattle are managed extensively, significant gross nutritional limitations are not typically observed in dairy systems because of the nutritional requirements for milk yield concurrent with pregnancy. While gross nutrient deficiencies may be slightly more likely during the dry period, it is possible that the dam will compensate and favour the developing fetus over her own needs. Specific nutrient deficiencies, however, may occur and alter development.

Choline is a nutrient that may be limiting in many situations, even when other nutrient needs are met in the dry cow. Supplementation to the cow in late gestation can significantly improve health and growth of the calf after parturition. As a collateral benefit, choline improves lactational performance of the dam. In a recent study, cows were supplemented with 60 grams of rumen protected choline (12.9 grams of choline ion) for 3 weeks before through 3 weeks after calving (Zenobi et al., 2018a, b). The objective was to test whether increased choline availability would improve aspects of calf health and performance, particularly those related to colostrum physiology. Calves were born to dams that were or were not supplemented with choline, and then were fed colostrum from either supplemented or non-supplemented dams such that four treatments were established: 1) choline in utero and no choline supplemented colostrum, 2) choline in utero and choline supplemented colostrum (positive control), 3) no choline in utero and no choline supplemented colostrum (negative control), and 4) no choline in utero and choline supplemented colostrum. Using that design allowed for assessment of the effects of in utero choline to be determined separate from the effect of ingestion with colostrum.

With regard to health, choline supplementation increased the survival of calves relative to that of non-supplemented calves, with the in utero and colostrum supplemented calves having the highest overall survival to 24 days of age. Calves that received in utero or colostrum choline were intermediate to the positive and negative controls. Part of that effect may have resulted from improved immunoglobulin G (IgG) uptake in the calves that received colostrum from supplemented dams, regardless of their in utero treatment. In contrast, in utero choline reduced the incidence of fever relative to the absence of choline. Calves from choline supplemented dams also showed less severe responses to challenge with lipopolysaccharide (LPS), which is a commonly used stimulator of immune responses. Collectively, these results suggest that choline supplementation to the dam improves immune status in the calf, especially when the calf is fed colostrum from the supplemented dam.

In addition to the impacts on calf health, choline treatment increased average daily gain through 300 days of life. This is likely because of an increase in consumption of milk in choline treated calves; however, choline also improved the intake of starter grain as calf age advanced. That improvement in starter intake should buffer the transition off milk at weaning, which may then reduce the lag associated with the shift from a liquid to a solid diet. More efficient feed utilization may also result from the modulation of immune sensitivity discussed above, wherein nutrients are partitioned to productive purposes in calves that received choline in utero compared with non-supplemented calves.

Disease Challenge of the Dam in Late Gestation

As discussed previously, challenge with the outer coat of the gram-negative bacteria *E. Coli* (i.e., LPS) is a commonly used proxy for an animal's response to a pathogen stimulus. Using this approach, Burdick Sanchez et al. (2017) and Carroll et al. (2017) investigated the effects of a late gestation LPS challenge of the dam on calf performance and the calf's response to similar LPS challenge after birth. Beef cows received a single, moderate dose of LPS or saline approximately 50 days before calving and were then monitored until parturition. Calf birth weights were not affected by in utero LPS exposure, but preweaning average daily gain and weaning weight were increased for calves exposed to in utero LPS compared with the control calves..
Heifer calves delivered by the LPS challenged and control cows were raised as a group under the same conditions and then subjected to an LPS challenge at ~240 days of age. A number of variables related to immune status were monitored in the heifers during the acute phase of the response to LPS to determine if in utero exposure would alter responses after birth. Basal vaginal temperature was not affected by in utero exposure to LPS. But the response of those heifers to LPS challenge did differ. Specifically, the heifers exposed to LPS in utero had a longer duration of fever after LPS challenge relative to the control animals. The extension of the fever was associated with a similar increase in sickness behaviour of the prenatal LPS heifers compared with the controls, which may indicate an increased risk for extended performance loss in calves.

In response to LPS, the body typically secretes signalling factors called cytokines to induce movement and activity of immune cells toward a pathogen insult. After LPS challenge, all heifers increased secretion of tumour necrosis factor-α (TNF-α), a potent cytokine, but the increase was similar for both groups. However, in utero LPS-exposed heifers secreted more interleukin-6 (IL-6) relative to the control heifers, suggesting greater sensitivity to a similar stimulus. Both TNF-α and IL-6 are important stimulators of fever responses, so the greater IL-6 secretion in in utero LPS heifers is consistent with the extended fever in those animals vs. controls. Whereas there was no treatment effect on total numbers of white blood cells or the proportion of monocytes to polymorphonuclear cells after LPS challenge, there were differences in certain cell markers that indicate an enhanced activation of leukocytes in the heifers that had been exposed to LPS in utero. Because energy is required for immune surveillance, greater sensitivity of the immune system may partition energy away from growth and other more productive endpoints while not enhancing disease resistance. Indeed, Burdick Sanchez et al. (2017) indicated in utero LPS-exposed heifers had significant reductions in energy and protein efficiency after the acute LPS challenge compared with control animals.

- **In utero Heat Stress Impacts on Health and Growth**

Heat stress in late gestation significantly reduces productivity of the dam in the next lactation, but perhaps of greater interest are the negative effects of in utero heat stress on multiple aspects of health, growth and performance of the developing fetus (reviewed in Dahl et al., 2017). In an effort to increase the capacity for heat exchange from the uterus to the external environment in cattle, heat stress increases uterine vascularity but not in a manner that increases nutrient and oxygen exchange with the fetus. Indeed, in utero heat stress compromises growth, likely because perfusion of the placenta is reduced. In addition, gestation length is shorter, thereby decreasing time for growth and possibly development in general. Thus, it is no surprise that calves born to heat stressed dams have lower bodyweights at birth.

For calves that experienced in utero heat stress, lower bodyweight persists through weaning and puberty relative to that of calves born to cooled dams. No difference in bodyweight is observed at maturity, which suggests that compensatory growth likely occurs from year 1 to 2 of life. But is also likely that composition of gain is not the same in heat stressed vs. cooled calves. Phenotypic observations that support the notion of differences in body composition include greater stature in cooled calves vs. those that endured in utero heat stress. Additionally, there are metabolic adaptations that favour energy partitioning to peripheral tissues in in utero heat stressed calves including elevated concentrations of insulin early in life, more rapid clearance of glucose following glucose challenge and slower clearance of insulin after an insulin challenge, the latter two being indicators of greater potential for movement of nutrients into peripheral tissue.

The negative impacts of in utero heat stress are not limited to growth and metabolism (reviewed in Dahl et al., 2019). Heat stressed calves have lower transfer of IgG compared with cooled calves, but there is little evidence of an effect on colostrum quantity of IgG. When the effects of in utero heat stress were compared with those of cooling by feeding both types of calves colostrum from the same source, IgG transfer remained lower in heat stressed calves. When calves born from cows that were housed under cool conditions were fed colostrum from either a heat stressed or a cooled dam, there was no difference in absorption of IgG, which provides further confirmation that it is not a colostrum-mediated effect.
Rather, more recent studies indicate that in utero heat stress accelerates gut closure, so there is less time for IgG transfer to occur. Within the first 24 to 36 hours of life, the initial layer of enterocytes lining the calf intestine rapidly degrades and sloughs off of the intestine, and the cells are replaced by new enterocytes that have tight junctions with the adjacent cells to limit transfer of large molecules across the gut; this is known as gut closure. Thus, we can use the relative rate of enterocyte death as an indicator of the speed of gut closure. In calves that experience in utero heat stress, this process appears to occur at a more rapid pace than that in calves born to cooled dams. That translates to an acceleration of closure that then reduces the amount of time for IgG uptake by the calf regardless of the source or quality of colostrum. Unfortunately, that also suggests that there is no way to manage that lower IgG uptake after birth.

The effects of lower immune status in heat stressed calves before weaning translate into poorer health as those calves grow. Indeed, calf loss from birth through first calving increases with in utero heat stress, indicating that health is compromised. There are also reductions in milk yield in the first lactation, but this is not growth-related because bodyweight at first parturition is the same regardless of in utero heat stress or cooling (reviewed in Dahl et al., 2019). However, as discussed earlier, the in utero heat stressed calves are likely less efficient from a milk production at maturity and have a higher fat composition of body mass. The heat stress effect continues to reduce yields in the second and third lactation relative to calves from cooled dams, suggesting that the heat stress impacts are permanent for that calf. There are significant changes in the methylation patterns that accompany in utero heat stress, which is a hallmark of imprinting or 'fetal programming' (Skibiel et al., 2018). Methylation is a mechanism whereby the efficiency of genetic signalling is altered without any change in the actual coding sequence of the gene. More importantly, methylation patterns are transmitted to those animal's offspring, and we have now observed that the reductions in performance are passed on to at least two subsequent generations (Almeida et al., 2019). This means that the effect of in utero heat stress continues to be a drag on performance and health long after the actual stressor has been removed.

- **Conclusions**

The preceding examples highlight the dramatic impact of changes within normal ranges of temperature, nutrient supply and disease exposure that alter performance and health outcomes long after the initial stimulus is gone. It is important to note that all these effects occurred during the last trimester of gestation, when it might be reasonable to expect less impact from a developmental standpoint on the developing fetus because of the older gestational age. Therefore, these studies highlight the importance of dry period management for positive outcomes on the dam, but perhaps more important and less explored, positive effects on the calf for life.

- **References**


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