A look at late-gestation and early post-partum developmental programming in beef cattle

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Abstract
The study of developmental programming in cattle productions has opened new possible opportunities for improved production practices through multi-generational feeding approaches. This use of nutritional stimuli during different stages of production has been shown to have influence on a variety of economically relevant traits in the beef sector, like reproduction, efficiency, and carcass traits. In beef production studying developmental programming is important not only as a proactive management approach for manipulating desirable offspring phenotype, but also as a reactive approach in attempt to overcome intentional stressors from the environment, such as drought, which may also impact offspring growth and performance potential. In late gestation in particular, adipogenesis is often the main target for developmental programming effects. However newer interests in late gestation maternal nutrition may impact colostrogenesis, resulting in lactocrine programming impacts on calf development and health. In this proceeding we will discuss our recent work on late gestation maternal nutrition impacts on developmental programming and impacts on colostrum and lactocrine programming effects. As research continues to increase the understanding of the impacts of maternal nutrition on future impacts of offspring production traits, this new management strategy may represent the next steps in improving efficiency, health, and production traits in the beef industry.

Introduction

Many beef producers have often noticed that the calf crop from certain years may have been a particular good year or poor year in calf performance. Although unbeknownst to those producers, they may have been noticing the impacts of fetal or developmental programming. This field of study has grown particularly from research in the 90's and 2000's from epidemiological data from health outcomes following of children of women pregnant during World War II famines (Rosebloom et al., 2001). This resulted in the general concept of developmental programming which suggests that early life stressors, such as nutritional, toxicological, environmental, etc. conditions, can alter offspring phenotypes later in life. These stressors can alter expression of a variety of genes and may even have lasting impacts that can be inherited from generation to generation. Generally, these effects on the offspring are largely a function of the timing of the stressor during fetal development.

For beef cattle some of these key developmental periods are outlined in Figure 1. There are many excellent published reviews on the potential of fetal/developmental programming as a transformative technology in the beef industry which covers these fetal programming impacts in more detail including Funston et al., (2010); Du et al., (2010); Robinson et al., (2013); Funston and Summers, (2013); Summers and Funston, (2013); Mossa et al., (2015); Du et al., (2017); Greenwood et al., (2017);

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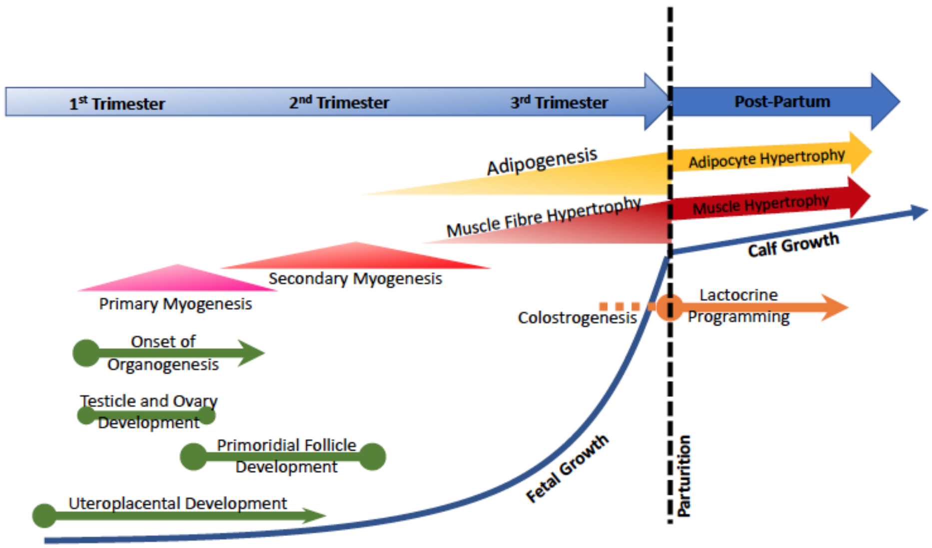

Figure 1: Key developmental timeline for economically relevant traits such as meat quality, reproductive development, growth and efficiency and their use as developmental programing in beef cattle. Partially adapted from Du et al., (2010)

Another key principle in the study of developmental programming is the theory of metabolic mis-match. This work is largely a result of British epidemiologist David Barker's "Thrifty Phenotype Hypothesis" where increased metabolic disease states were observed in adults born from mothers following severe nutritional restriction during mid-to-late pregnancy (Hales and Barker, 1992). This hypothesis describes a miss-match between the nutritionally restricted *in utero* environment in which the developing fetus was exposed, and the affluent nutritional environment in which offspring are raised. This mismatch primes the genetics of the fetus to expect a nutrient limiting environment, but the offspring does not encounter such hardships post-partum, resulting in improved metabolic efficiencies and increased fat deposition. Although this is a negative health outcome for humans, for the beef industry increased fat deposition and low metabolic rate are desirable characteristics. Therefore, in late gestation where adipogenesis occurs, many developmental programming approaches in beef cattle follow this metabolic miss-match approach.

Late Gestation Developmental Programming

Although there are many reasons to investigate developmental programming in early and mid gestation, from a practical management point of view for beef producers, cows are often managed more intensively as they approach parturition, meaning that a more proactive approach to developmental programing may be easier to implement during this period. During late gestation, maternal nutritional requirements increase exponentially to meet the increasing demands of the fetus and reproductive tissues (Bauman and Currie, 1980). Global nutrient restriction models or research focusing on protein or energy restriction/oversupply alone have been shown to influence developmental programming in late gestation. Many of the mechanisms controlling these developmental programming strategies are not well understood. However, previous research has indicated differential impacts on some key genes which are known to influence growth and efficiency, and adipose and muscle development. For example, research investigating insulin-like growth factor gene families impact muscle growth in cattle both pre- and postnatally (Brameld et al., 2000; Costello, et al., 2008; Micke et al., 2011).

Some previous research in late-gestation global nutritional restriction developmental models use a severe nutritional restriction model to illicit metabolic mis-match (Hough et al., 1990; LeMaster et al., 2017; Meyer et al., 2021). However, one major concern with severe nutritional restriction is the subsequent negative outcomes on the dam, where milk production, post-partum recovery and reproductive success of low BCS cows can be negatively impacted. However, previous work by our group found that nutrient restriction does not need to be severe in order to obtain fetal differences consistent with the thrifty phenotype hypothesis (Paradis et al., 2017). In a group of cows fed either free-choice (140% of total energy requirements) or restricted (85% of total requirements) from ~150 to d 250 of gestation, fetal tissue from longissimus dorsi or semitendinosus had mRNA expression differences in IGF related genes consistent with the theory of nutritional miss-match. Similarly to the results of the studies listed above, methylation of regions of IGF-2 (DMR2) and feed restriction reduced expression of micro RNAs associated with IGF-2 (miR-1, miR-133a) in longissimus dorsi tissue, suggesting that these genes are responsive to maternal nutritional intervention. This indicates that even mild nutrition restriction can influence developmental programming effects.

Often during mid-to-late gestation cattle are managed on native range or extended grazing systems, which may be deficient in protein during this developmental period. Previous developmental programming studies suggest supplemental protein in mid-to-late gestation also improves lipogenic carcass traits in beef cattle as reported by Larson et al., (2009); Underwood et al., (2010); Shoup et al., (2015); Summers et al., (2015); Wilson et al., (2016) and reviewed by Ladeira et al., (2018). Although there are a variety of mechanisms which may be involved in the developmental programming response, peroxisome proliferator-activated receptor gamma, a nuclear receptor which plays a role in adipogenesis and cellular lipid uptake and known to increase intramuscular fat (Baik et al., 2017). Differences in PPARG mRNA expression were reported in fetal *longissimus dorsi* from restricted fed cows in late gestation (Duarte et al., 2014; Paradis et al., 2017;). Additionally, our work showed a time by treatment effect from birth to weaning of heifer calves born from cows fed at or 140% of protein in an isocaloric diet, requirements for 9 weeks prepartum, where PPARG expression in muscle biopsies increased significantly more than heifers born from cows fed at requirements (Hare et al., 2019), suggesting that oversupply may also influence developmental programming.

Although protein supplementation strategies may elicit developmental programming effects, fewer studies have investigated amino acids, such as methionine, specifically. Methionine is a nutritional strategy of interest, as maternal diets high in methyl donors have been shown to alter DNA-methylation in skeletal muscle of calves (Liu et al., 2021). Therefore, these nutritional intervention strategies show potential as an intervention strategy which influences economically important traits for both the cow-calf producer (increased weaning weights) and feedlot producers (improved carcass traits). Although more research has focused on pre-partum intervention strategies, the post-partum period also represents an opportunity to influence development of the offspring. In dairy calves born from dams supplemented with rp-methionine had improved growth to weaning and increased the percentage of calves with acceptable passive transfer of IgG (Wang et al., 2021), suggesting that calf health status may also benefit from supplemental methionine. Supplemental amino acids has shown to increase milk production, protein, and fat content in beef cows (Hess et al., 1998). Recently, work from our group (Collins, 2019; Leivre, 2020-cow effects; Action et al., 2020, 2020a-feedlot performance) invested the impact of late gestational supply of protein and methionine on calf heath, growth, and performance traits. Cows were fed isocaloric diets at 90, 100, or 110% of total metabolizable protein requirements, with or without rumen protected methionine for 8 weeks before parturition. An additional group of cows were fed hay ad libitum, with or without 12g/hd/d rp-methionine, and subsequent steer offspring were evaluated in the feedlot (Action et al., 2020a). In both studies, despite limited number of steers, found differences in steer offspring performance or carcass traits. In protein restricted fed cows, steer offspring had increased weaning weights, and increased grade fat and lean yield, despite no significant differences in feedlot efficiency or performance. In the applied study, steer offspring from cows supplemented with rp-methionine, did not differ in feedlot performance, but were heavier at all pre-weaning time-points and upon entering the feedlot.

Energy requirements pre-partum also greatly increase prior to parturition (Bauman and Currie, 1980). Glucose is a particularly high demand metabolic fuel during this time as the growing calf uses most of the cow's available glucose. In our previous work investigating protein supplementation during late gestation beef heifers, we observed that their capacity to digest starch decreases as they approach calving (Hare et al., 2019), raising concern as to how adequately late gestation cattle can use the starch in their rations to meet their glucose requirements prior to calving. By comparison, late gestation dairy cows are anticipated to enter into a glucose deficit immediately prior to calving when they are consuming energy in excess of their requirements (Overton, 1998). Since dairy cattle typically consume more energy dense rations during their dry period, collectively this led us to question whether beef cows are experiencing a glucose shortage before calving and whether their metabolism and colostrum production would shift when they received more dietary energy.

At the Ontario Beef Research Center, we fed primi- (n = 47) and multiparous (n = 109) cattle rations that were formulated with CNCPS 6.55 (Nutritional Dynamic System software, RUM&N Sas, Via Sant' Ambrogio, Italy) to provide 80 (LowME, n = 54), 100 (ConME, n = 51) or 120% (HighME, n = 51) of their predicted metabolizable energy requirements for 56 days prior to calving. At calving, colostrum was sampled for composition and bottle fed back to calf. Performance was similar amongst treatments prior to calving; although, HighME cattle consistently lost body weight and condition at a lesser rate than LowME cattle before calving. Feeding more energy prior increased serum glucose and cholesterol while reducing serum NEFA concentrations, indicating that markers of energy balance were altered between treatments. Part of this response is likely due to LowME cattle being in a negative energy balance and mobilizing more adipose tissue to meet energy requirements. However, we also found that the HighME cattle were less insulin responsive than the LowME cattle during glucose tolerance tests, demonstrating that alternate pathways of energy repartitioning were activated by differential energy provision. As anticipated, cattle that consumed more energy prior to calving produced more colostrum (HighME: 2.6 ± 0.31 kg; ConME: 2.1 ± 0.25 kg; LowME: 1.5 ± 0.17 kg). Increasing energy intake increased the lactose concentration, while decreasing the crude protein, urea, and beta-hydroxybutyrate concentration. Colostrum fat concentration was greatest for the LowME treatment relative to the ConME (6.1 vs. 4.9 ± 0.29%), but the HighME colostrum fat concentration (5.5 ± 0.29%) did not differ from either the LowME or ConME. Colostrum immunoglobulin G concentration decreased linearly from low to high ration energy density. However, because the HighME cattle produced more colostrum yield, component yield (fat, protein, lactose, and immunoglobulin G) was uniformly increased when more energy was provided. Lastly, calf birth body weight and preweaning average daily gain were unaffected by prepartum metabolizable energy supplementation. (Croft et al., 2022; Hare et al., 2022a). Collectively these data demonstrate that beef cattle colostrum production is influenced by metabolizable energy consumption prior to calving. In addition, they demonstrate that, when beef cattle experience mild energy deficits, they will hierarchically prioritize calf development before colostrogenesis and maintaining their own body reserves; however, colostrum production is prioritized above body maintenance.

Post-Partum Lactocrine Programming

Although historically colostrum has been studied more for its implications on passive transfer of immunity and subsequent impacts on calf health, there are numerous bioactive components contained in colostrum, which may have implications for calf growth. Many of these bioactive components have functions for not only immune development, but also have roles as hormones and growth factors, which may have play important signaling rolls in early growth and development (Tacoma et al., 2017). Although little is known about beef colostrum specifically, changes bioactive concentrations between colostrum and the next subsequent milkings in dairy cattle are highlighted in Blum and Hammon., (1999). Although this work and others (reviewed by Fischer-Tlustos et al., 2020) illustrates the shifting composition as colostrum matures into milk, less known is on how pre-partum maternal nutrition impacts the profile of the colostrum and abundance of other bioactives in colostrum, particularly in beef cattle.

Our previous work on late gestation protein supplementation where crossbred Hereford heifers fed isocaloric diets either 100% of predicted metabolizable protein (MP) requirements (n=7; CNCPS) or 133% predicted metabolizable protein requirements (n=6) for 55 ± 3 d prior to parturition. Protein supplementation decreased colostrum fat % (3.4 vs 7.0 $\pm$0.8; P=0.003) and tended to decrease net energy content (1.4 vs.1.7 $\pm$0.1; P=0.052) of colostrum (Hare et al., 2019). Progeny were followed until 112 d of age, however, no treatment differences in heifer calf performance was observed, although age x treatment interactions were observed for PPARg expression in muscle, as discussed above. From this study we also investigated shifts in the proteome (Radford, et al., 2018) and lipidome (Wood, unpublished). Colostrum analysis identified 213 distinct proteins, of which 11 were enriched and 13 were depleted in cows fed a high MP diet vs controls. Enriched colostrum proteins were associated with gut and immune system development (5.48E-08 < P < 2.49E-4) and depleted colostrum proteins were significantly associated with growth regulation (5.48E-08 < P < 2.49E-4). To investigate if bioactives were transferred into calf serum, serum samples from progeny 6 h post-colostrum consumption identified 179 distinct proteins, of which 60 were common with colostrum. In calf serum, maternal dietary protein treatment enriched 28 and depleted 19 proteins compared to progeny from control fed dams. These proteins were distributed across 27 interdependant interaction networks. However, generally maternal protein supplementation decreased generalized inflammatory proteins and non-specific macrophage stimulation and promoted a precision response immune system. Lipidomic analysis determined 1629 lipids in colostrum, which differences in maternal protein supplementation resulted in > 2-fold difference in 246 phospholipids, 103 sphingolipids, 69 storage lipids within colostrum. Although this study has a limited number of animals, it clearly demonstrates the major impact of pre-partum nutrition on colostrum composition and passive transfer of bioactive compounds can be impacted by maternal diet in beef cattle. Further research is needed in the area to elucidate if these differences in bioactives influence longer-term offspring efficiency, health, and carcass traits

One colostrum bioactive of particular interest in lactocrine programming is insulin, as colostrum insulin concentrations can be over 10-fold greater in colostrum that in milk (Fischer-Tlustos et al., 2020) and 50 to 100 times greater than circulating blood concentration in dairy cows (Mann et al., 2016) and can be in influenced by late gestation nutrition in dairy (Mann et al., 2016) and beef (Hare et al., 2022) cows. These greater colostrum insulin concentrations are hypothesized to influence gut development in calves (Shamir et al., 2005). In a recent study (Hare et al., 2023) in dairy bull calves supplemented with a colostrum replacer at either 5x or 10x basal (control) colostrum insulin concentrations, and slaughtered 30 h post- initial colostrum consumption. Dry rumen mass decreased and duodenal dry tissue weight increased with increasing insulin concentration, where ileal villi height and surface area and lactose activity in jejunum also increased with increasing insulin concentration. However, ileal isomaltase activity decreased with increasing colostrum insulin. After the second meal increased colostrum insulin supplementation, increased glucose absorption and NEFA clearance rates, and insulin clearance rates. Although this study is short term, it does demonstrate that changes in colostrum bioactives can have impacts on gut development, which can lead to small changes in postprandial metabolism. Further research is needed to determine if these short-term changes can lead to longer term implications for increase absorptive capacity, improved efficiency and growth and if these same results are observed in beef cattle.

In conclusion, there are clear impacts of late gestation nutrition, induced by global nutrient restriction, protein supplementation, and energy supply which can impact offspring performance, and gene expression of key genes. New investigations into the impact of late gestation nutrition on colostrum composition may also impact offspring development and growth. As new findings in this field of study continue, these results may open up new management regimes for beef producers in late-gestation, which may have positive impacts on offspring growth, health, carcass traits and production efficiency.

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