



Impacts of Nutritional Management During Early Postnatal Life on Long-Term Physiological and Productive Responses of Beef Cattle

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Effective early postnatal nutritional management is a crucial component of livestock production systems, and nutrient manipulation during this period has been shown to exert long-term consequences on beef cattle growth and physiology. Metabolic imprinting defines these biological responses to a nutritional intervention early in life that permanently alter physiological outcomes later in life. Early weaning has been used to study metabolic imprinting effects, given that it allows for nutritional manipulation of animals at a young age. This practice has been shown to enhance carcass characteristics in feedlot cattle and accelerate reproductive development of females. Another strategy to study the effects of metabolic imprinting without the need for early weaning is to provide supplements *via* creep feeding. Providing creep feed to nursing cattle has resulted in transient and long-term alterations in cattle metabolism, contributing to increased reproductive performance of developing heifers and enhanced carcass quality of feeder cattle. Collectively, results described herein demonstrate nutrient manipulation during early postnatal life exerts long-term consequences on beef cattle productivity and may be a strategy to optimize production efficiency in beef cattle systems.

Keywords: beef cattle, early weaning, metabolic imprinting, production, supplementation

INTRODUCTION

Food production will need to increase considerably in the next decades to meet the demand of a growing population [Food and Agricultural Organization (FAO), 2009]. As such, beef cattle are an integral component of achieving food security, and development of efficient and sustainable management strategies are fundamental to reach a level of animal production that can provide for the population by 2050 [Food and Agricultural Organization (FAO), 2009]. The success of each cow-calf operation depends upon proper establishment and maintenance of optimal developmental trajectory of the offspring (Bartol et al., 2013). Producers are also challenged to improve growth, efficiency, carcass weight and quality (Robinson et al., 2013); traits that benefit carcass value (USDA, 1997) and beef palatability. Moreover, efficient reproductive outcomes are essential for successful production systems, of which development of replacement beef heifers are a vital component. The embryonic, fetal, and neonatal periods are the stages of life in which most developmental processes occur, and manipulating nutritional status during these critical periods presents an opportunity to

modulate future growth and performance trajectory (Fall, 2011; Koletzko et al., 2012). Therefore, understanding and exploiting metabolic cues responsible for programming offspring growth, health, and performance is warranted.

Developmental programming, also referred to as fetal programming, is the concept that alterations in nutrient or endocrine status during critical prenatal development stages may result in adaptations that permanently alter the trajectory of growth, physiology, and metabolism of the offspring (Barker and Clark, 1997; Wu et al., 2006). However, organ development and tissue differentiation are not complete at birth in most mammals and these processes extend into the early postnatal period. Several regulatory mechanisms and biological processes are also functionally immature at birth and continue development postnatally (Srinivasan and Patel, 2008). In fact, young animals can respond to environmental stimuli that are foreign to their normal development through adaptations at the cellular, biochemical, and molecular levels (Patel and Srinivasan, 2011). The ability of organisms to diverge from a developmental program leads to alternate developmental trajectories and therefore divergent phenotypes, metabolism, and physiology (Bateson et al., 2004). The potential for environmental stimuli to induce these changes tends to be greatest during early in life, when cells and tissues are still differentiating (Hochberg et al., 2011). The term metabolic imprinting defines these biological responses to a nutritional intervention occurring during a limited period of susceptibility in early postnatal life, which permanently alters physiological outcomes later in life (Patel and Srinivasan, 2011). Research described herein focuses on interventions applied before the animal reaches 9 months of age. This concept has substantial implications for animal agriculture, and nutritional strategies targeted at these critical periods of development should be explored to optimize production efficiency and profitability in beef cattle systems.

POTENTIAL MECHANISMS OF DEVELOPMENTAL PROGRAMMING

Nutrient supply may permanently affect an organism's structure or function of tissues through a variety of mechanisms, such as induced variations in organ structure, altering cell number or rate of proliferation, clonal selection, and epigenetics (Lucas, 1991). Modifications in organ vascularization due to altered nutrient supply during organogenesis may affect the ability of cells to generate and respond properly to stimuli including circulating nutrients or hormonal signals (Waterland and Garza, 1999). Therefore, local concentrations of nutrients and metabolites present during organogenesis may result in morphologic alterations, permanently affecting body function. Rates of cellular proliferation and growth has been shown to be tissue-specific, indicating that different tissues have diverse and limited periods of hyperplastic and hypertrophic growth (Winick and Noble, 1966; MacIntosh et al., 2006). Given that cell growth is dependent on nutrient supply, nutrient deprivation or excess during essential periods of proliferation may affect rate of cell division, leading to permanent changes in cell number. For

example, maternal nutrient restriction results in a reduction in the total number of secondary muscle fibers (Zhu et al., 2004), whereas maternal overnutrition results in increased number and size of adipocytes in postnatal skeletal muscle (Yan et al., 2013). The process of myogenesis occurs *in utero*, and postnatal muscle growth is dictated by an increase in muscle fiber size, absent of formation of new muscle fibers (Stickland, 1978). Hence, nutrient supply during critical periods of development exerts profound effects on muscle growth and development during postnatal life (Neiberger and Johnson, 2012).

Proliferation of cells within all organs involves the initial multiplication of a finite population of founder cells. As this process unfolds, early genetic and epigenetic modifications occur within individual cells, distinguishing them from subpopulations of rapidly dividing cells (Waterland and Garza, 1999). However, nutrients such as vitamins and minerals are vital components of enzymes and proteins involved in DNA synthesis, repair, and maintenance of genome integrity (Neiberger and Johnson, 2012). Therefore, altered nutrient supply may result in incorrect base pairing during replication and subsequent effects on cellular metabolism which will be inherited by daughter cells (Waterland and Garza, 1999; Fenech, 2010). These differences among proliferating cells are the basis for clonal selection, resulting in similar populations of rapidly dividing cells that develop distinct metabolic characteristics resulting from diverse microenvironmental conditions (Waterland and Garza, 1999). The phenomenon of metabolic imprinting can also occur through epigenetics referring to alterations in gene expression due to changes in chromatin structure (Wu et al., 2006). Similar to the epigenetic alterations associated with fetal programming, metabolic imprinting also results in postnatal silencing or activation of genes occurring independent of changes in DNA sequence (Lucas, 1998; Funston and Summers, 2013). These changes can pass from one cell generation to another via mitotic inheritance, as well as from one generation of a species to the next via meiotic inheritance (Ling and Groop, 2009). More specifically, epigenetic mechanisms elicited by dietary factors include DNA methylation, histone modifications, and non-coding microRNA (Canani et al., 2011). As examples, dietary restriction of folate, vitamin B12, and methionine, which serve as methyl donor molecules, in the diet of the gestating ewe resulted in widespread alterations in DNA methylation patterns and impaired immune function in the offspring (Sinclair et al., 2007). Dietary restriction of protein in maternal diets results in reduced DNA methylation and histone modification in offspring, persisting into adulthood (Lillicrop et al., 2007, 2008).

EVIDENCE OF METABOLIC IMPRINTING IN CATTLE

Evidence of metabolic imprinting has been well-established in multiple species including mice, humans, pigs, and dairy cattle. Postnatal nutrient restriction impairs skeletal muscle growth and delays muscle fiber maturation in piglets (Hu et al., 2020), whereas newborn rodents reared on high carbohydrate formulas display altered expression of hypothalamic genes that regulate

appetite later in life, leading to persistent body weight gain and intake (Srinivasan et al., 2008). In humans, increased energy intake at four months of age lead to greater weight gain and body mass index later in childhood (Ong et al., 2006). Additionally, research in dairy cattle shows enhancing nutrient intake of calves during the pre-weaning phase increased milk production during their first lactation compared to calves that were limit fed (Soberon and Van Amburgh, 2013).

Metabolic Imprinting in Early-Weaned Beef Calves

In beef cattle research, early-weaning (EW) is defined as separating calves from their dams prior to 180 days of age (Rasby, 2007), and has been used to study the effects of metabolic imprinting, given that it allows for nutritional manipulation of animals at a young age. This management practice is usually applied during periods of forage shortage to alleviate the amount of nutrients required by postpartum cows to support lactation (Arthington and Minton, 2004). This decrease in nutritional requirements combined with the removal of the negative feedback of calf suckling leads to improved cow reproductive efficiency, particularly for first and second parity females (Arthington and Kalmbacher, 2003; Arthington and Minton, 2004). Calves older than 60–90 days of age can acquire most of their nutrient requirements from solid feed (Maddox, 1965), thus providing nutrient dense diets at the time of EW may optimize calf development as well. Research demonstrates enhanced growth performance of EW calves compared to normally weaned cohorts (Gasser et al., 2006a; Waterman et al., 2012a,b; Scheffler et al., 2014).

Long-term effects of calf-management following EW on growth and carcass quality of beef steers have been reported (Myers et al., 1999; Meyer et al., 2005; Waterman et al., 2012b; Moriel et al., 2014a; Scheffler et al., 2014), primarily due to early exposure to a high-concentrate diet. Calves provided a high-concentrate diet at 177 vs. 231 days of age had improved feed efficiency while in the feedlot, enhanced marbling scores, heavier carcasses, and a greater percentage of carcasses grading Choice or better (Myers et al., 1999). Likewise, calves that were early-weaned at 3 to 4 months of age and consuming a high-concentrate diet produced heavier carcasses with enhanced marbling scores compared to forage-fed, normally weaned cohorts (Scheffler et al., 2014). These outcomes can be attributed to enhanced expression of adipogenic genes, resulting in early differentiation of adipocytes and fatty acid accumulation (Schoonmaker et al., 2003). To further explore this rationale, Moriel et al. (2014a) investigated the impact of duration of exposure to a high-concentrate diet following EW at 2 to 3 months of age on growth performance, muscle gene expression, and carcass traits of *Bos indicus*-influenced beef steers. Steers were either normally weaned at 250 days of age (NW; day 180 of the study), or EW at 70 days of age (day 0 of the study) and then randomly assigned to 1 of 3 EW management systems: (1) EW and grazed on pasture for 180 days (EWRG); (2) EW and limit-fed a high-concentrate diet for 180 days (EW180); EW and

TABLE 1 | Muscle mRNA expression of genes associated with growth and adipose tissue development in beef steers developed in different calf management systems from the time of early weaning (d 0)¹.

Item ³	Treatment ²			
	NW	EW180	EW90	EWRG
IGF1				
d 90	0.63	1.42	1.30	1.05
d 180	1.02	1.45	0.87	1.18
IGF1R				
d 90	0.71 ^a	2.00 ^c	1.46 ^b	0.59 ^a
d 180	1.02 ^a	1.45 ^b	0.87 ^a	0.82 ^a
PPAR- γ				
d 90	0.90 ^{ab}	1.41 ^{bc}	1.93 ^c	0.53 ^a
d 180	1.95 ^a	4.59 ^b	1.06 ^a	0.57 ^a

¹Adapted from Moriel et al. (2014a), and values within a row with different superscripts (a,b,c) differ ($P \leq 0.05$). ²NW = steers remained with cows until d 180; EW180 = steers early-weaned and limit-fed a high-concentrate diet until d 180; EW90 = steers early-weaned and metabolically imprinted, by limit-feeding a high-concentrate diet until d 90, then grazed on pastures until d 180; EWRG = steers early-weaned, grazed on pastures until d 180. ³Values are expressed as relative fold-change compared with threshold cycle of reference genes analyzed within the same sample. IGF1R, IGF-1 receptor, PPAR- γ , peroxisome proliferator-activated receptor- γ .

limit-fed a high-concentrate diet for 90 days and then grazed on pasture for 90 days (EW90).

In muscle samples collected on day 90, Moriel et al. (2014a) reported greater mRNA expression of *IGF-I receptor* (IGF1R) for EW180 and EW90 steers compared to EWRG and NW steers (Table 1). Additionally, in muscle samples collected on d 180, IGF1R mRNA expression was greater for EW180 vs. EW90 steers and EWRG steers and intermediate for NW steers (Table 1) (Moriel et al., 2014a). As cattle grow, muscle accretion is positively correlated with circulating concentrations of IGF-1 and IGF1R density (Oksbjerg et al., 2004), therefore, the increased mRNA expression of IGF1R in muscle of EW steers exposed to a high concentrate diet immediately after weaning provided additional binding sites for local and systemic IGF-1, resulting in enhanced growth performance of EW vs. NW steers (Moriel et al., 2014a). Moreover, in muscle samples collected on day 90, Moriel et al. (2014a) reported mRNA expression of *peroxisome proliferator-activated receptor γ* (PPAR- γ) was greater for EW180 and EW90 steers compared to EWRG steers, but similar between EW180 and NW steers, whereas muscle mRNA expression of PPAR- γ on day 180 was greater for EW180 vs. NW, EW90, and EWRG steers (Table 1) (Moriel et al., 2014a). Expression of PPAR- γ is associated with adipogenesis of bovine intramuscular adipose tissue (Lim et al., 2011) and plays a pivotal role regulating adipogenesis through induction of genes mediating lipid metabolism (Houseknecht et al., 2002). Hence, Moriel et al. (2014a) concluded that early exposure to high-concentrate diets not only enhanced growth performance of EW steers, but also induced early differentiation of adipocytes as evidenced by greater mRNA expression of PPAR- γ compared to normal weaning. Corroborating these results, Graugnard et al. (2010) reported exposure to diets rich in starch for 112 days

following EW induced precocious intramuscular preadipocyte differentiation and lipid filling in muscle tissue of steers, through elevated expression of PPAR- γ and its targets. More specifically, these authors reported greater mRNA expression of PPAR- γ targets including sterol regulatory element binding factor 1 over 100 days after steers were fed a common diet, suggesting a nutritional imprinting effect elicited by early exposure to high dietary starch, leading to enrichment of intramuscular adipocytes as the animal matured (Grauagnard et al., 2010). Conversely, steers fed a diet low in starch showed a blunted lipogenic response through upregulated expression of anti-adipogenic factors, and delayed insulin sensitivity (Grauagnard et al., 2010).

Recently, specific nutrient inputs provided to EW calves have been investigated including lipid supplements rich in omega-6 fatty acids. Mangrum et al. (2016) demonstrated early-weaned beef steers supplemented with calcium salts of soybean oil (CSSO) had greater percentage of lipid in striploin steaks, and enhanced marbling scores upon slaughter. Further, supplemented steers had decreased average adipocyte diameter in intramuscular adipose tissue, with a greater percentage of intramuscular adipocytes in the small diameter range (Mangrum et al., 2016). Essential fatty acids such as linoleic acid are precursors for activation of receptor/ligand systems that initiate expression of binding proteins (Gaillard et al., 1989), subsequently enhancing expression of PPAR- γ (Xu et al., 1999; Thoennes et al., 2000), thereby regulating adipogenesis. Adipocytes grow by both hyperplasia and hypertrophy, with the latter occurring as cattle age and terminally differentiated cells fill with lipid (Cianzio et al., 1985). Hence, these authors concluded that CSSO supplementation to EW steers enhanced early adipocyte hyperplasia and differentiation (Mangrum et al., 2016). Accordingly, Tipton et al. (2020) also reported increased adipocyte hyperplasia in intramuscular adipose tissue of EW steers supplemented with CSSO for 90 days, evidenced by decreased adipocyte diameter. The same result was not evident in traditionally weaned steers provided the same supplementation, indicating that providing CSSO supplementation earlier in life may result in a greater number of undifferentiated stem cells driven toward adipogenic confirmation and differentiation (Tipton et al., 2020).

Long-term effects of calf management following EW on growth and reproductive performance of beef heifers have been investigated as well (Gasser et al., 2006a,b,c,d; Moriel et al., 2014b). Cow-calf systems rely on replacement heifers to initiate and maintain estrous cyclicity, and in order for heifers to be efficacious, they need to attain puberty by 12 months of age and conceive early in the breeding season (Perry and Cushman, 2013). A plethora of factors play a role in heifer development and puberty attainment, the most notable of which are genetics and nutritional management (Perry, 2016). Most of the research evaluating the impact of nutrition on age at puberty has focused on nutritional inputs after weaning at 7 months of age (Funston et al., 2012). However, the potency of nutritional interventions may be greater earlier in life during critical developmental windows (Day and Anderson, 1998; Hochberg et al., 2011). For example, the effects of nutrition during the early maturation period were evaluated by Gasser et al. (2006a,b,c,d). This model

consisted of EW at 2 to 4 months of age and feeding a high-concentrate diet. These authors demonstrated that enhancing the average daily gain (ADG) of EW heifers resulted in hastened puberty attainment and increased the percentage of heifers achieving precocious puberty (Gasser et al., 2006d). Further, ovarian maturation was accelerated in EW heifers offered a high-concentrate diet, evidenced by increased frequency of LH pulses, dominant follicle diameter, and follicular wave duration (Gasser et al., 2006c). These studies were conducted using *B. taurus* breeds, whereas few studies have investigated the influence of nutritional status during early postnatal development on reproductive maturation in *B. indicus*-influenced breeds, which often reach puberty at older ages compared to *B. taurus* heifers (Rodrigues et al., 2002).

To address this gap in knowledge, Moriel et al. (2014b) investigated the impact of post-EW nutritional management strategy on growth and puberty attainment of *B. indicus*-influenced heifers. Heifers were either normally weaned at 250 days of age (NW; day 180 of the study) or EW at 70 days of age (day 0 of the study) and randomly assigned to 1 of 3 EW management systems: (1) EW and grazed on pasture for 180 days (EWRG); (2) EW and limit-fed a high-concentrate diet for 180 days (EW180); EW and limit-fed a high-concentrate diet for 90 days and then grazed on pasture for 90 days (EW90). These authors reported body weight (BW) was greater for EW180 and EW90 heifers compared to EWRG and NW heifers until day 90 after EW. However, at the time of normal weaning (day 180 of the study), EW180 heifers were the heaviest, EWGR were the lightest, and EW90 and NW were intermediate and did not differ between each other (Moriel et al., 2014b). Consequently, cumulative percentage of pubertal heifers at the start of the breeding season was greatest for EW180 heifers and did not differ between EWRG and NW heifers (**Figure 1**) (Moriel et al., 2014b). More importantly, the cumulative percentage of pubertal heifers at the start of the breeding season was nearly 2-fold greater for EW90 compared to NW heifers, despite their similar BW and ADG from day 180 until 390 of the study, which provides further evidence of the metabolic imprinting effects of early exposure to high-concentrate diets in beef cattle. Similar findings have been reported using *B. indicus*-influenced heifers, weaned at approximately 4 months of age and fed a high concentrate diet to promote a body weight gain of 1 kg daily (Cardoso et al., 2014a,b). Cardoso et al. (2014b) employed a stair-step dietary strategy involving alternating periods of feed restriction and re-feeding in heifers weaned at 3.5 months of age. These authors reported heifers exhibiting high rates of body weight gain between 4 and 6.5 months of age, followed by feed restriction between 6.5 to 9 months of age attained puberty at similar rates compared to cohorts receiving a high-concentrate diet continuously Cardoso et al. (2014b). Alternatively, the same results were not observed in heifers that were subjected to feed restriction from 4 to 6.5 months of age, followed by access to a high-concentrate diet Cardoso et al. (2014b). Moriel et al. (2014b) concluded that the enhanced nutrient intake and ADG of EW90 heifers during a period of developmental plasticity, hastened follicular development and LH secretion (Gasser et al., 2006c,d), contributing to accelerated reproductive maturation.

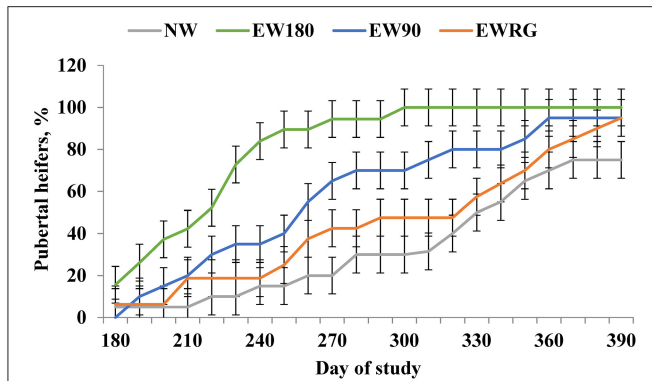


FIGURE 1 | Puberty achievement of replacement heifers developed on different calf management systems from the time of early-weaning (d 0) until the time of normal weaning (d 180). NW = heifers remained with cows until d 180; EW180 = heifers early-weaned and limit-fed a high-concentrate diet until d 180; EW90 = heifers early-weaned and metabolically imprinted, by limit-feeding a high-concentrate diet until d 90, then grazed on pastures until d 180; EWRG = heifers early-weaned, grazed on pastures until d 180. A treatment \times day interaction ($P < 0.01$) was detected for puberty attainment. Adapted from Moriel et al. (2014b).

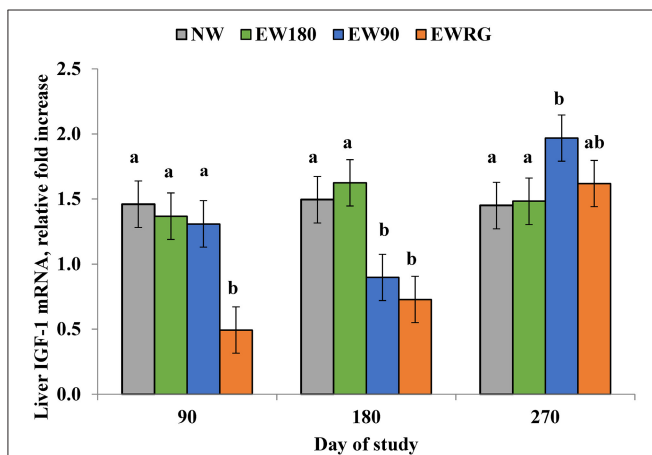


FIGURE 2 | Liver IGF-1 mRNA expression of heifers developed on different calf management systems from the time of early-weaning (d 0) until the time of normal weaning (d 180). NW = heifers remained with cows until d 180; EW180 = heifers early-weaned and limit-fed a high-concentrate diet until d 180; EW90 = heifers early-weaned and metabolically imprinted, by limit-feeding a high-concentrate diet until d 90, then grazed on pastures until d 180; EWRG = heifers early-weaned, grazed on pastures until d 180. Adapted from Moriel et al. (2014b). A treatment \times day interaction was detected ($P < 0.01$). ^{a,b}Within days, means without a common superscript differ ($P \leq 0.05$).

Moriel et al. (2014b) also reported that hepatic mRNA abundance of IGF-1 on d 90 was positively correlated ($P \leq 0.05$) with the ADG from d 0 to 90, whereas liver IGF-1 mRNA expression on d 180 was positively correlated ($P = 0.0002$) with the ADG from d 90 to 180. Moreover, liver IGF-1 mRNA expression of EW90 heifers on d 270 (90 days after all heifers were provided similar nutritional management) was greater than NW and EW180 heifers (Figure 2), despite the similar post-weaning ADG, which further supports the concept of metabolic

imprinting effects on puberty achievement of beef heifers. Dietary regimens that promote high rates of body weight gain result in greater adiposity and increased circulating concentrations of leptin, insulin, and IGF-1 compared with heifers achieving lower rates of body weight gain (Allen et al., 2012; Cardoso et al., 2014b; Alves et al., 2015). These changes in circulating metabolites result in modifications in the reproductive neuroendocrine axis such as increased pulse frequency of GnRH and LH (Cardoso et al., 2014a) and enhance steroidogenesis within the ovaries (Spicer and Echternkamp, 1995). Moriel et al. (2014b) reported age at puberty decreased approximately 0.5 days for every 1 ng/mL increase in plasma concentrations of IGF-1 on d 90 and 180, providing evidence that the metabolic imprinting process, likely via IGF-1 hastened puberty attainment of beef heifers. Further, increased rates of body weight gain in heifers following EW has resulted in altered DNA methylation patterns in the hypothalamic arcuate nucleus, with significant modifications in the methylation status of genes associated with growth and puberty attainment (Alves et al., 2017), indicating the potential for neuronal plasticity. Collectively, these results demonstrate there exists a critical period in which nutrient inputs may induce early activation of the reproductive axis, thus programming puberty attainment in beef heifers.

Metabolic Imprinting in Normally Weaned Beef Calves

While EW provides an opportunity to manipulate calf nutrient intake during a critical window of development and increase cow productivity (Arthington and Kalmbacher, 2003; Arthington and Minton, 2004), this strategy may not be a feasible management alternative for many commercial cow-calf systems depending on forage availability, supplement cost, and overall net return (Vendramini et al., 2006). Thus, alternative management strategies to enhance early life nutrition and growth of nursing calves are warranted. For example, post-weaning injections of bovine somatotropin (bST) hastened puberty attainment of replacement beef heifers (Cooke et al., 2013), whereas circulating IGF-1 during juvenile development has been positively associated with puberty attainment (Moriel et al., 2014b). Hence, Piccolo et al. (2018) investigated the impact of pre-weaning injections of bST on growth and reproductive performance of *B. taurus* \times *B. indicus* beef heifers. Heifers received a s.c. injection of a saline solution or 250 mg of bST every 14 days from 134 to 162 days of age (Piccolo et al., 2018). Piccolo et al. (2018) reported pre-weaning injections of bST decreased age at puberty in heifers by approximately 26 days and hastened puberty attainment and pregnancy rates compared to saline injections, despite similar growth performance and nutritional management from weaning and during the breeding season. Contrariwise, Moriel et al. (2019) reported decreased puberty attainment in Nelore heifers (*B. indicus*) receiving pre-weaning bST injections (25% vs. 40% for bST and saline heifers, respectively). Inconsistencies between the two experiments were attributed to greater baseline plasma IGF-1 concentrations in *B. indicus* females compared with to *B. taurus* crosses (Alvarez et al., 2000; Moriel et al., 2019). This likely led to an overstimulation of the somatotrophic axis following

bST injections in Nelore heifers (Cooke et al., 2020), which was detrimental to reproductive maturation (Moriel et al., 2019), emphasizing the importance of developing metabolic imprinting strategies specific to cattle subspecies.

Another alternative to isolate the effects of metabolic imprinting and EW is to provide supplements to nursing cattle via creep feeding (CF). This practice serves to adapt calves to concentrate supplementation prior to weaning, and it is well-established that BW at weaning may be increased if limited or unlimited CF supplementation is offered to nursing calves (Faulkner et al., 1994; Sexten et al., 2004; Moriel and Arthington, 2013a,b). Creep-fed calves also exhibit greater dry matter intake (Faulkner et al., 1994; Moriel and Arthington, 2013b) and BW gain during the feedlot receiving period (Arthington et al., 2008), which is one of the most critical periods in the beef production cycle when cattle are exposed to a variety of challenges resulting in increased rates of morbidity (Snowder et al., 2006). Therefore, strategies to enhance nutrient intake during this period are warranted to optimize receiving cattle performance (Cooke, 2017). For example, CF calves experience decreased morbidity and mortality during transition to the feedlot (e.g., 7–10 months of age) compared to cohorts receiving no pre-weaning supplementation (Loerch and Fluharty, 1999; Myers et al., 1999; Lardy and Maddock, 2007). Research examining the impacts of CF and finishing performance and carcass traits has been variable. In a two-year study, Lancaster et al. (2007) observed CF calves had greater carcass weights, dressing percentage, and backfat thickness compared to non-supplemented calves in the first year but not the second. Others have also reported no differences in carcass traits comparing calves provided or not CF supplementation (Tarr et al., 1994; Myers et al., 1999; Shike et al., 2007; Gadberry et al., 2012).

The inconsistency in lifelong effects associated with pre-weaning nutrient supply on carcass quality may be due to a variety of confounding factors across experiments including post-weaning management, and composition and intake of nutrients during CF. However, nutrient specific strategies, such as supplemental fat, warranted investigation given the roles endogenous fatty acids play in adipogenesis (Price et al., 2000; Houseknecht et al., 2002). Supplementation with CSSO after weaning has resulted in increased marbling and percent choice carcasses upon slaughter compared with non-supplemented cohorts (Cooke et al., 2011; Mangrum et al., 2016). However, such dietary inputs offered earlier in life may be even more beneficial, given that developmental plasticity declines as animals mature (Lucas, 1998). In a 2 × 2 factorial design, Schubach et al. (2019) investigated the impacts of CSSO supplementation to beef steers at 2 months of age via CF and/or during a 40-day preconditioning period on carcass development and quality. Treatments were formulated to be isocaloric and isolipidic but differing in fatty acid profile. These authors observed steers receiving CSSO via CF supplementation had greater mRNA expression of *adipocyte fatty acid binding protein-4*, *fatty acid synthase* (FASN), PPAR- γ , and *stearoyl CoA desaturase* in muscle samples collected during feedlot finishing compared with cohorts that received prilled saturated fat during CF (Table 2). Expression of these genes did not differ between all calves before shipping to the feedlot,

TABLE 2 | Carcass traits and expression of genes in the longissimus muscle associated from beef steers supplemented with Ca salts of soybean oil (CSSO) or prilled saturated fat (CON) from 2 to 4 months of age via creep feeding^{1,2}.

Item	CON	CSSO
Carcass traits		
Hot carcass weight, kg	359	364
Ribeye area, cm ²	80.0	79.3
Yield grade	3.48	3.55
Marbling	793	470
Backfat, cm	1.50	1.52
Gene mRNA expression ³		
Adipocyte fatty acid binding protein		
Shipping	66.7	54.3
Finishing	38.5 ^b	72.5 ^a
Fatty acid synthase		
Shipping	91.0	80.2
Finishing	124 ^b	210 ^a
Peroxisome proliferator-activated receptor- γ		
Shipping	7.18	6.11
Finishing	5.01 ^b	8.20 ^a
Stearoyl-CoA desaturase		
Shipping	65.8	61.8
Finishing	96.5 ^b	202 ^a

¹Adapted from Schubach et al. (2019) and values within a row with different superscripts (a,b) differ ($P \leq 0.05$). ²Samples were collected via needle biopsy prior to shipping to the feedlot after a 40-day preconditioning period (shipping) and once during the feedlot period (finishing). ³Values are expressed as relative fold-change compared with threshold cycle of reference genes analyzed within the same sample.

whereas differences were only noted during the feedlot period, when calves were exposed to high-energy diets and lipogenesis is substantial (Pethick et al., 2004; Schubach et al., 2019). However, supplementing CSSO during a 40-day preconditioning period had no impact on muscle gene expression during the feedlot period, whereas providing CSSO during both CF and preconditioning did not yield additive benefits (Schubach et al., 2019). These authors concluded that CSSO supplementation provided via CF, during a period of elevated epigenetic and developmental plasticity (Lucas, 1998), elicited alterations in mRNA expressions of genes associated with adipogenic activities in the muscle, which was suggestive of a metabolic imprinting effect (Du et al., 2010). However, differential gene expression during the feedlot period did not translate into differences in performance or carcass traits upon slaughter, which did not differ between treatments (Table 2) (Schubach et al., 2019). These results are contrary to those reported by Cooke et al. (2011) and Mangrum et al. (2016), whereas the treatments offered in the previous experiments were not isocaloric or isolipidic as utilized by Schubach et al. (2019). Nonetheless, elevated mRNA expression may not be accompanied by equivalent phenotypic responses (Clancy and Brown, 2008; Graugnard et al., 2010), and research is still warranted to investigate the effects of CSSO supplementation to nursing beef cattle on adipogenesis and lipid metabolism (Schubach et al., 2019).

TABLE 3 | Body composition and mRNA expression of genes associated with lipogenesis and growth in beef heifers receiving (MI) or not (CON) a corn-based supplement *ad libitum* from 2 to 4 months of age *via* creep feeding^{1,2}.

Item	CON	MI
Body composition		
Backfat thickness, mm	4.14	4.20
<i>Longissimus</i> muscle depth, mm	46.7	47.3
Adipocyte morphometry		
Area μm	2920	3202
Density cells/mm	253	240
Gene mRNA expression ³		
Adipose tissue		
Peroxisome proliferator-activated receptor- γ	1.93 ^b	2.40 ^a
Fatty acid synthase		
Day 51	40.7 ^b	527 ^a
Day 111	64.0	219.8
Day 261	776	730
Day 325	925	977
Hepatic tissue		
Insulin-like growth factor I	62.9 ^b	83.4 ^a

¹Adapted from Reis et al. (2015) and values within a row with different superscripts (a,b) differ ($P \leq 0.05$). ²Samples were collected on days 0, 51, 111, 187, 267, and 325 of the experiment. ³Values are expressed as relative fold change compared with threshold cycle of reference genes analyzed within the same sample. A treatment \times day interaction was detected for mRNA expression of fatty acid synthase ($P = 0.08$); therefore, means are reported and separated within each sampling day.

Numerous studies have shown reductions in age at puberty in heifer calves offered a high plane of nutrition early in juvenile development (Shamay et al., 2005; Gasser et al., 2006a; Davis Rincker et al., 2011; Cardoso et al., 2014b; Moriel et al., 2014b) due to advanced conditioning and maturation of the reproductive axis (Kelly et al., 2020). However, these experiments have been conducted using EW, and research exploring the effects of early-life nutritional status while suckling on growth and puberty attainment is limited. Providing nursing beef heifers access to CF supplementation to increase pre-weaning ADG may also affect their future lactation potential. For example, nursing heifers receiving CF supplementation beginning at 4 months (Buskirk et al., 1996a) or 5 months (Buskirk et al., 1996b) of age had decreased milk production as primiparous cows, which was attributed to greater fat accumulation in the mammary gland (Brown et al., 2005). Conversely, Sexten et al. (2004) reported heifers offered CF supplements containing 18% CP had greater milk production 52 and 108 days postpartum compared to heifers fed supplements containing 14% CP, suggesting increasing dietary CP may alleviate the negative effects of accelerated BW gain during the pre-weaning period on mammary gland development. However, pre-weaning body weight gain and weaning body weight was similar between calves born from creep-fed and non-creep fed heifers (Buskirk et al., 1996b; Sexten et al., 2004), suggesting calves are able to compensate for decreased milk production from the dam by increasing forage intake (Sexten et al., 2004).

In an effort to avoid the critical allometric period of mammary gland growth (Buskirk et al., 1996a), and yet still initiate metabolic imprinting events, Reis et al. (2015) provided nursing beef heifers *ad libitum* access to CF supplementation (MI) or not (CON) from 68 to 118 days of age. These authors reported MI heifers had transient and long-term increases in genes regulating adipocyte development (Reis et al., 2015). More specifically, MI heifers had increased adipocyte mRNA expression of FASN following the imprinting phase and long-term increased mRNA expression of PPAR- γ during the entire experimental period compared to CON heifers (Table 3) (Reis et al., 2015). These authors reported no differences in backfat thickness or subcutaneous adipocyte size and density (Table 3), despite the established role both genes play in adipocyte development (Grauagnard et al., 2009; Lim et al., 2011). Furthermore, MI heifers had long-term increased hepatic mRNA expression of IGF-1 (Table 3), whereas plasma IGF-1 concentrations increased only transiently following the imprinting phase. Treatment differences noted for mRNA expression of genes associated with nutrient and lipid metabolism between MI and CON heifers were suggestive of metabolic imprinting effects due to CF supplementation during a critical window of development (Reis et al., 2015). Guggeri et al. (2018) also reported providing CF supplementation to nursing beef heifers beginning at 75 days of age resulted in long-term increases in hepatic and endometrial mRNA expression. More specifically, heifers receiving CF supplementation had greater hepatic mRNA expression of growth hormone receptor and IGF binding protein-3 on day 7 of their estrous cycle, and greater endometrial mRNA expression of IGF-1 on day 16 of their estrous cycle compared to non-supplemented cohorts (Guggeri et al., 2018). Such expression in the endometrium is consistent with ewes carrying larger embryos (Sequeira et al., 2016) and is related to embryo growth and uterine function in dairy cows (Wathes et al., 2011). Therefore, Guggeri et al. (2018) concluded that early life nutritional status programmed the sensitivity of the liver to growth hormone, and resulted in long-term effects on the functioning of the somatotrophic axis in the endometrium.

Reis et al. (2015) noted that puberty attainment did not differ between MI vs. CON heifers, corroborating similar circulating IGF-1 concentrations and body composition (Table 3) given these variables influence advancement of puberty onset (Schillo et al., 1992; Cooke et al., 2008). As mentioned, others have reported hastened puberty attainment in EW heifers receiving a high-concentrate for 70 days (Gasser et al., 2006a) and 90 days (Moriel et al., 2014b); therefore, Reis et al. (2015) concluded that perhaps a longer period of CF supplementation for nursing beef heifers may be required to substantially increase their supplement intake and effectively enhance their reproductive development. Corroborating this rationale, Guggeri et al. (2014) reported that providing CF supplementation to nursing beef heifers from 75 to 158 days of age resulted in accelerated puberty attainment compared to unsupplemented, traditionally weaned cohorts, as well as EW heifers. Collectively, these results demonstrate that providing CF supplementation to nursing heifers during a critical window of development may induce early activation of the reproductive axis.

CONCLUSIONS

Metabolic imprinting is associated with a critical window of postnatal developmental plasticity in which nutritional interventions may result in long-term consequences on animal metabolism (Patel and Srinivasan, 2011). Identifying and implementing strategies targeting this period of development offers an opportunity to enhance efficiency and profitability of beef production systems. Early-weaning of beef calves prior to the breeding season is a strategy that may increase reproductive performance of primiparous cows, but simultaneously optimize carcass quality of feeder cattle and reproductive development of replacement females. Providing supplement to nursing calves via CF may be a nutritional alternative to stimulate metabolic imprinting effects, without the need for EW. Collectively, the results from the experiments described herein

demonstrate that manipulating nutrient supply during periods of developmental plasticity, such as early postnatal life, exerts long-term consequences on performance and physiology of beef cattle.

AUTHOR CONTRIBUTIONS

KH, RC, and PM: conceptualization, writing—original draft preparation, writing—review, and editing. RC: supervision. All authors contributed to the article and approved the submitted version.

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