

## **FETAL PROGRAMMING: IMPLICATIONS FOR BEEF CATTLE PRODUCTION**

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### **Introduction**

The concept of fetal programming, also known as developmental programming, was first hypothesized using human epidemiological data in which environmental stimulus in utero resulted in altered long term development, growth and disease susceptibility in children from undernourished mothers during the Dutch famine (Barker et al., 1993). Recently, literature regarding fetal programming effects in domesticated livestock has been reviewed (Funston et al., 2010a; Ford and Long, 2012).

Many factors influence livestock nutrient requirements including breed, season, and physiological function (NRC, 2000). Fetal programming responses can result from a negative nutrient environment, which can be caused by 1) breeding of young dams who compete for nutrients with rapidly growing fetal systems; 2) increased incidences of multiple fetuses or large litters; 3) selection for increased milk production, which competes for nutrients with increased energy demand from fetal and placental growth; or 4) breeding of livestock during high environmental temperatures and pregnancy occurring during periods of poor pasture conditions (Wu et al., 2006; Reynolds et al., 2010). Studies have reported instances of compromised maternal nutrition during gestation resulting in increased neonatal mortality, intestinal and respiratory dysfunction, metabolic disorders, decreased postnatal growth rates, and reduced meat quality (Wu et al., 2006). Proper management of cow nutrition during gestation can improve progeny performance and health.

### **Placental Development**

The bovine placenta attaches along the uterine wall at locations known as caruncles. These knob-like structures along the uterine luminal surface serve as attachment sites for the chorionic villi of the fetal placenta known as cotyledons. The caruncle-cotyledonary unit, also known as a placentome, serves as the primary functional area of physiological exchange between mother and fetus (Funston et al., 2010a). Establishment of functional uteroplacental and fetal circulation is one of the earliest events during embryonic and placental development (Patten, 1964; Ramsey, 1982) allowing for transportation of all respiratory gas, nutrient, and waste exchanges between the maternal and fetal systems (Reynolds and Redmer, 1995; 2001). The efficiency of transport is related to uteroplacental blood flow (Reynolds and Redmer, 1995) and although placental growth slows during the last half of gestation, blood flow to the placenta increases three to fourfold from mid to late gestation to support the exponential rate of fetal growth (Rosenfeld et al., 1974; Reynolds et al., 1986; Metcalfe et al., 1988; Ferrell, 1989; Reynolds and Redmer, 1995).

Due to the importance of placental development on fetal nutrient transfer, studies have been conducted to determine how maternal nutrition can influence placental development, or placental programming. Zhu et al. (2007) reported nutrient restriction of beef cows from day 30 to 125 of gestation resulted in reduced ( $P < 0.05$ ) caruncular and cotyledonary weights from nutrient restricted cows compared to control, unrestricted cows, and fetal weights from nutrient restricted cows tended ( $P = 0.12$ ) to be reduced compared to control cows. Following

realimentation during day 125 to 250 of gestation, caruncular and cotyledonary weights were still reduced for nutrient restricted cows; however, fetal weight was not different. Vonnahme et al. (2007), using the same cows, reported increased placental angiogenesis as well as angiogenic factor mRNA abundance in the caruncular and cotyledonary tissues at the end of the nutrient restriction period. It was hypothesized the lack of significant fetal weight differences in regard to maternal nutrient restriction may have resulted from the increase in cotyledonary arteriolar density allowing for adequate nutrient transfer (Vonnahme et al., 2007; Zhu et al., 2007).

To measure capillary vascularity of the cotyledon, 4 measurements are collected: capillary area density (**CAD**), a flow-related measure; capillary number density (**CND**), an angiogenesis-related measure; capillary surface density (**CSD**), a nutrient-exchange measure; and area per capillary (**APC**), a capillary density per cross section of muscle area. Vonnahme et al. (2007) reported no difference in these 4 measures from day 30 to day 125 of gestation; however, from day 125 to 250, there were significant differences in CAD, CND, and CSD when comparing control and nutrient restricted cows, suggesting capillary area, numbers, and surface densities had been hindered upon realimentation. Nutrient restriction from day 30 to 125 of gestation in cows did not alter the vasculature of the bovine placenta; however, placental function must have been compromised due to reduced fetal weights.

### **Fetal Organ Development**

Robinson et al. (1977) reported 75% of ruminant fetal growth occurs during the last 2 months of gestation. Due to the minimal nutrient requirement during early gestation, inadequate nutrition during this time was thought to have little significance. However, during the early phase of fetal development critical events for normal conceptus development occur, including differentiation, vascularization, fetal organogenesis, and as previously mentioned, placental development (Funston et al., 2010a).

Fetal organ formation occurs simultaneously to placental development with limb development occurring as early as day 25 of gestation. Following limb development is a sequential development of other organs including the pancreas, liver, adrenal glands, lungs, thyroid, spleen, brain, thymus, and kidneys (Hubbert et al., 1972). Testicle development begins by day 45 in male calves, and ovarian development begins in female calves by day 50-60. Another important event in female gonadal development occurs approximately day 80 of gestation when oocyte nests break down to form primordial follicles (Nilsson and Skinner, 2009). These follicles represent the oocyte supply available to a female after puberty known as the ovarian reserve, which can influence her reproductive lifespan (Hirshfield, 1994). A review by Caton et al. (2007) lists fetal programming examples in livestock models of individual organs including heart (Han et al., 2004), lung (Gnanalingham et al., 2005), pancreas (Limesand et al., 2005; 2006), kidney (Gilbert et al., 2007), placenta (Reynolds et al., 2006), perirenal fat (McMillin et al., 2004; Matsuaki et al., 2006), and small intestine (Greenwood and Bell, 2003).

### **Fetal Muscle Development**

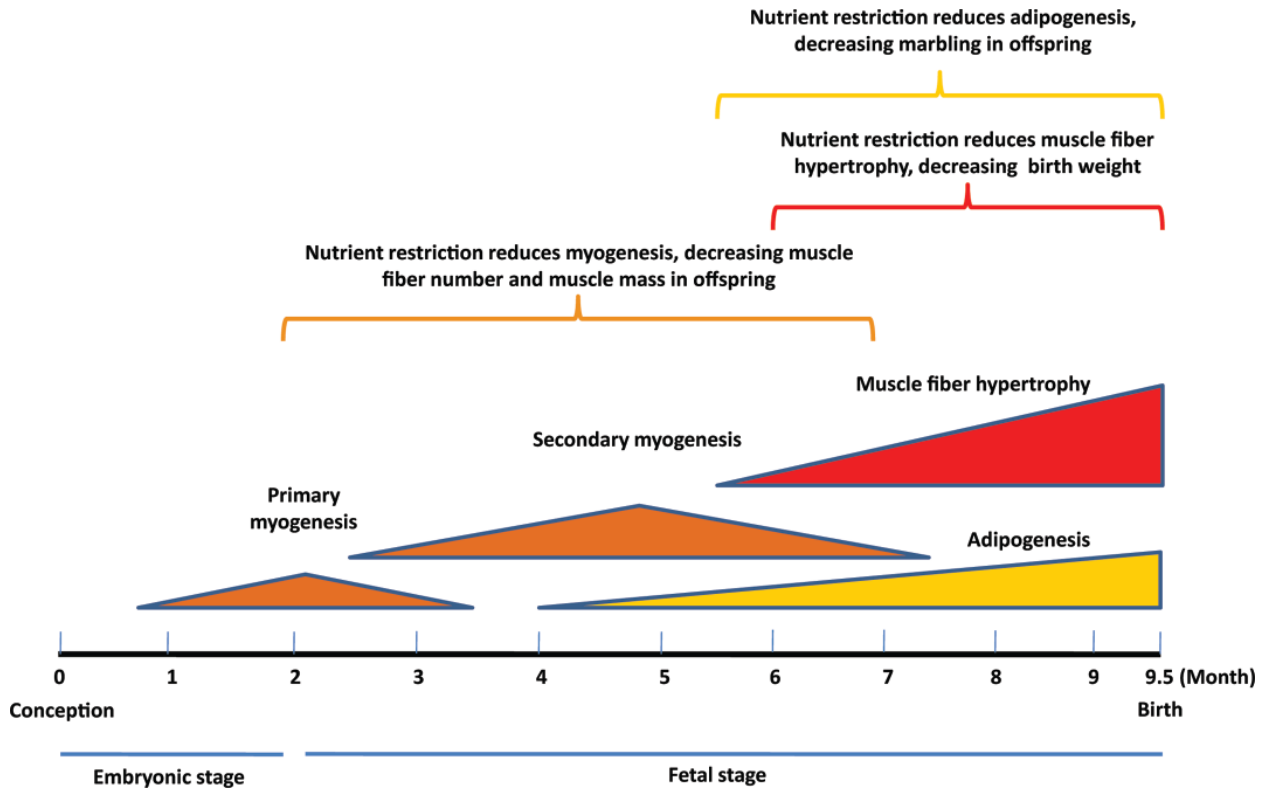
The fetal stage is also crucial for skeletal muscle development because muscle fiber numbers do not increase after birth (Stickland, 1978; Zhu et al., 2004). Skeletal muscle is a lower priority in nutrient partitioning compared with the brain, heart, or other organ systems

(Bauman et al., 1982; Close and Pettigrew, 1990), making it particularly vulnerable to nutrient deficiency. Thus, a decrease in nutrient availability to the dam during gestation can result in a reduced number of muscle fibers through fetal programming, reducing muscle mass and impacting animal performance. Both muscle fiber number and intramuscular adipocytes, which provide the sites for intramuscular fat accumulation or marbling formation, are influenced during fetal development (Tong et al., 2008; Du et al., 2010).

Figure 1 depicts the effects of maternal nutrition on fetal skeletal muscle formation and control points in which maternal nutrition has been shown to impact fetal muscle development. Although primary muscle fibers of the bovine fetus begin forming within the first 2 months of gestation (Russell and Oteruelo, 1981), very limited numbers of muscle fibers are formed at this stage; thus, maternal nutrition has little influence on primary muscle formation during this early time frame (Du et al., 2010). During the second to eighth month of gestation, the majority of muscle fibers form; therefore, reduction of muscle fiber formation during this stage through any source of stimuli (e.g., maternal nutrition) has long-lasting, irreversible consequences to the offspring (Du et al., 2010). The prospect of nutritional management's altering marbling may be greatest for the fetal stage, due to its importance in adipocyte formation, followed by the neonatal stage, early weaning stage (i.e., 150–250 days of age), and finally, weaning and older stages (Du et al., 2010).

Larson et al. (2009) reported increased progeny birth weights from protein supplemented dams, suggesting a potential alteration in fetal muscle growth. Greenwood et al. (2009) reported steers from cows nutritionally restricted during gestation had reduced body weight and carcass weight at 30 months of age compared to steers from adequately fed cows. Both Larson et al. (2009) and Greenwood et al. (2009) reported a retail yield on a carcass weight basis was greater in steers from nutrient restricted cows, indicating an increased propensity for carcass fatness was not a consequence of nutritional restriction in utero.

Although fetal adipocyte development begins early in gestation, the majority of fetal adipose tissue is not deposited until the final few weeks of gestation (Symonds et al., 2007). Adipose tissue growth occurs through preadipocyte proliferation, impacting formation of new mature adipocytes (hyperplasia); and increased size and lipid storage capacity of mature adipocytes (hypertrophy). By feeding ewes 150% of NRC nutrient requirements, Tong et al. (2008, 2009) reported increased adipogenesis in fetal skeletal muscle. In a review on fetal programming of skeletal muscle, Du et al. (2010) reported when University of Wyoming scientists fed beef cattle 1 of 3 diets: 100%, 70% of NRC (2000) nutrient requirements, or 70% of NRC (2000) nutrient requirements plus supplementation of ruminal bypass protein from day 60 to 180 of gestation, steer progeny from dams fed 70% nutrient requirements plus supplement had numerical decreases in marbling scores when compared to steers from dams fed 100% of requirements. Underwood et al. (2010) also reported increased tenderness in steers from dams grazed on improved pasture compared to steers from dams grazed on native range during mid-gestation.



**Figure 1.** Effects of maternal nutrition on bovine fetal skeletal muscle development. Dates are estimated mainly based on data from studies in sheep, rodents, and humans and represent progression through the various developmental stages. Nutrient restriction during midgestation reduces muscle fiber numbers, whereas restriction during late gestation reduces both muscle fiber sizes and the formation of intramuscular adipocytes. From Du et al. (2010).

### Heifer Progeny Performance

Data regarding the effect of late gestation protein supplementation on heifer progeny performance are reported in Table 1. Martin et al. (2007) conducted a study with cows grazing dormant Sandhills range during late gestation. One group received a 42% CP (DM basis) cube offered 3 times weekly at the equivalent of 1.0 lb/day while another group received no supplement. Calf birth weight between heifer progeny from supplemented and nonsupplemented dams was not different; however, heifer progeny from supplemented cows had increased adjusted 205 day weaning weights, prebreeding weight, weight at pregnancy diagnosis, and improved pregnancy rates compared to heifers from nonsupplemented dams. Martin et al. (2007) also reported after a subset of these heifers were placed in a Calan gate individual feeding system, DMI, ADG, and residual feed intake between heifer progeny from supplemented and nonsupplemented dams was not different.

Funston et al. (2010b), using the same cow herd, offered a distillers based supplement (28% CP, DM basis) 3 times weekly at the equivalent of 1.0 lb/day, or no supplement during late gestation as cows grazed either dormant Sandhills range or corn crop residue. Calf weaning weight was greater ( $P = 0.04$ ) for heifers from protein supplemented dams, whereas Martin et al. (2007) reported a trend ( $P = 0.12$ ) for increased weaning weight for heifers from protein supplemented dams. Funston et al. (2010b) also reported a decreased age at puberty for

heifers from protein supplemented cows and a trend ( $P = 0.13$ ) for higher pregnancy rates when compared to heifers from nonsupplemented dams, possibly related to decreased age at puberty. Similarly, Corah et al. (1975) reported heifers born to primiparous heifers fed 100% of their dietary energy requirement during the last 90 days of gestation were pubertal 19 days earlier than heifers born to primiparous heifers fed 65% of their dietary energy requirement.

**Table 1.** Effect of maternal protein supplementation on heifer progeny performance

Item	Dietary treatment			
	Martin et al. (2007) <sup>1</sup>		Funston et al. (2010b) <sup>2</sup>	
	NS	SUP	NS	SUP
Weaning BW, lb	456	467	492 <sup>a</sup>	511 <sup>b</sup>
Adj. 205-d wt, lb	481 <sup>a</sup>	498 <sup>b</sup>	470	478
DMI, lb/d	14.39	14.88	20.89	20.50
ADG, lb/d	0.90	0.88	1.86 <sup>x</sup>	1.74 <sup>y</sup>
Residual Feed Intake	-0.12	0.07	0.08	-0.04
Age at Puberty, d	334	339	365 <sup>x</sup>	352 <sup>y</sup>
Pregnant, %	80 <sup>a</sup>	93 <sup>b</sup>	83	90

<sup>1</sup>NS = dams did not receive protein supplement while grazing dormant Sandhills range during the last third of gestation; SUP = dams were supplemented 3 times per week with the equivalent of 1.0 lb/d of 42% CP cube (DM basis) while grazing dormant Sandhills range during the last third of gestation.

<sup>2</sup>NS = dams did not receive protein supplement while grazing dormant Sandhills range or corn residue during the last third of gestation; SUP = dams were supplemented 3 times per week with the equivalent of 1.0 lb/d of a 28% CP cube (DM basis) while grazing dormant Sandhills range or corn residue during the last third of gestation.

<sup>a,b</sup>Means within a study with different superscripts differ ( $P \leq 0.05$ ).

<sup>x,y</sup>Means within a study with different superscripts differ ( $P \leq 0.10$ ).

Funston et al. (2010b) reported no differences in heifer weight at prebreeding and no differences in calf birth weight, calf production, or second calf rebreeding when comparing heifer progeny from supplemented and nonsupplemented cows. Gunn et al. (1995) reported a decrease in the proportion of singleton, and an increase in the proportion of multiple births over three parities in progeny born to ewes offered a protein supplement while grazing native pastures during the last 100 days of gestation compared to progeny from nonsupplemented ewes. Late gestation supplementation did not alter the proportion of barren ewe progeny (Gunn et al., 1995). Martin et al. (2007) reported a 28% increase in the proportion of heifers calving in the first 21 days of the calving season from protein supplemented dams compared to heifers from nonsupplemented dams. Pryce et al. (2002) reported no difference in progeny heifer reproductive performance when considering dairy cow maternal nutritional status, determined by BCS, DMI, and milk yield of fat and protein.

### Steer Progeny Performance

As previously mentioned, studies have reported improved muscle development in steers from adequately fed dams when compared to progeny from nutrient restricted dams. Underwood et al. (2010) reported increased weight gains, final weight, and hot carcass weight in steers from cows grazing improved pasture from day 120 to 180 of gestation when compared to progeny from cows grazing native range during that same time (Table 2). Steers from cows grazing improved pasture had increased back fat and tended to have improved marbling scores compared to steers from cows grazing native range.

To determine the effect dietary energy source had on progeny calf performance, Radunz (2009) offered cows 1 of 3 diets during gestation beginning on approximately day 209 of gestation: hay (fiber), corn (starch), or distillers grains with solubles (fiber plus fat). Corn and distillers grains diets were limit fed to ensure isocaloric intake among treatments. Results indicated reduced birth weights for calves from dams fed grass hay when compared to calves from the other two groups (Table 2), with an increase ( $P \leq 0.05$ ) in calf body weight reported through weaning when comparing calves from corn fed dams to hay fed dams. Feedlot performance among treatments was not different; however, calves from hay fed dams required 8 and 10 more days on feed to reach a similar fat thickness when compared to calves from distillers and corn fed dams, respectively.

**Table 2.** Effect of maternal nutrition on steer progeny performance

Item	Dietary treatment				
	Underwood et al. (2010) <sup>1</sup>		Radunz (2009) <sup>2</sup>		
	NR	IP	Hay	Corn	DDGS
Birth BW, lb	85	81	86 <sup>a</sup>	95 <sup>b</sup>	91 <sup>b</sup>
Weaning BW, lb	534 <sup>a</sup>	564 <sup>b</sup>	580 <sup>a</sup>	607 <sup>b</sup>	591 <sup>a,b</sup>
ADG, lb/d	3.28 <sup>a</sup>	3.65 <sup>b</sup>	3.37	3.46	3.41
HCW, lb	726 <sup>a</sup>	768 <sup>b</sup>	688	688	675
12-th rib fat, in	0.49 <sup>a</sup>	0.65 <sup>b</sup>	0.48	0.50	0.51
Marbling score <sup>3</sup>	420	455	549 <sup>a</sup>	506 <sup>b</sup>	536 <sup>ab</sup>

<sup>1</sup>NR = dams grazed native range from day 120 to 180 of gestation; IP = dams grazed improved pasture from day 120 to 180 of gestation.

<sup>2</sup>Hay = dams offered a diet of grass hay beginning on day 209 of gestation; Corn = dams offered limit-fed diet of corn beginning on day 209 of gestation; DDGS = cows offered a limit-fed diet of distillers grains with solubles beginning on day 209 of gestation.

<sup>3</sup>Where 400 = Small<sup>0</sup>.

<sup>a,b</sup>Means within a study with different superscripts differ ( $P \leq 0.05$ ).

Stalker et al. (2006, 2007) reported steer progeny from dams supplemented the equivalent of 1.0 lb/day (42% CP, DM basis) cube during late gestation had no difference in calf birth weight when compared to steers from nonsupplemented dams. Conversely, Larson et al. (2009) using the same cow herd, reported an increase in calf birth weight when comparing calves born to dams supplemented the equivalent of 1.0 lb/day (28% CP, DM basis) cube during late gestation to calves from nonsupplemented dams. In the study reported by Stalker et al. (2006), cows were utilized in a switchback design, whereas cows utilized by Larson et al. (2009) remained on the same treatment over the 3 year study.

Protein supplementation during late gestation increased weaning weight, ADG to weaning, and proportion of calves weaned when comparing calves from supplemented to nonsupplemented dams grazing dormant winter range (Stalker et al., 2006, 2007; Larson et al., 2009; Table 3). Stalker et al. (2006) reported no differences in steer progeny feedlot performance and carcass characteristics when comparing progeny from supplemented and nonsupplemented dams. However, Larson et al. (2009) reported increased ADG, HCW, and marbling scores in steers from supplemented dams. Furthermore, a greater proportion of steers from supplemented dams graded USDA Choice and USDA Choice or greater when compared to steers from nonsupplemented dams. Nonsupplemented cows in Larson et al. (2009) may have been under greater nutritional stress than Stalker et al. (2006) as average weaning date was approximately one month later and possibly had greater impact on fetal development.

**Table 3.** Effect of maternal protein supplementation of steer progeny performance

Item	Dietary treatment					
	Stalker et al. (2007) <sup>1</sup>		Stalker et al. (2006) <sup>1</sup>		Larson et al. (2009) <sup>2</sup>	
	NS	SUP	NS	SUP	NS	SUP
Weaning BW, lb	463 <sup>a</sup>	489 <sup>b</sup>	463 <sup>a</sup>	476 <sup>b</sup>	514 <sup>a</sup>	529 <sup>b</sup>
DMI, lb/d	24.6 <sup>a</sup>	26.6 <sup>b</sup>	18.7	18.8	19.8 <sup>x</sup>	20.3 <sup>y</sup>
ADG, lb/d	3.53	3.70	3.46	3.44	3.66	3.75
Feed:gain	6.97	7.19	5.41	5.46	5.37	5.38
HCW, lb	765 <sup>a</sup>	805 <sup>b</sup>	800	814	805 <sup>a</sup>	822 <sup>b</sup>
Choice, %	-	-	85	96	71	85
Marbling score <sup>3</sup>	449	461	467	479	445 <sup>a</sup>	492 <sup>b</sup>

<sup>1</sup>NS = dams did not receive protein supplement while grazing dormant Sandhills range during the last third of gestation; SUP = dams were supplemented 3 times per week with the equivalent of 1.0 lb/d of 42% CP cube (DM basis) while grazing dormant Sandhills range during the last third of gestation.

<sup>2</sup>NS = dams did not receive protein supplement while grazing dormant Sandhills range or corn residue during the last third of gestation; SUP = dams were supplemented 3 times per week with the equivalent of 1.0 lb/d of a 28% CP cube (DM basis) while grazing dormant Sandhills range or corn residue during the last third of gestation.

<sup>3</sup>Where 400 = Small<sup>0</sup>.

<sup>a,b</sup>Means within a study with different superscripts differ ( $P \leq 0.05$ ).

<sup>x,y</sup>Means within a study with different superscripts differ ( $P \leq 0.10$ ).

### Influence of Maternal Nutrition on Progeny Health

Several reports have linked maternal nutrition during gestation to calf health, including Corah et al. (1975), indicating increased morbidity and mortality rates in calves born to primiparous heifers receiving 65% of their dietary energy requirement over the last 90 days of gestation compared to calves from primiparous heifers receiving 100% of their energy requirement. One factor contributing to increased morbidity and mortality is decreased birth weight. Calves born to nutrient restricted dams were 4.5 lbs lighter at birth compared to calves from dams receiving adequate nutrition (Corah et al., 1975). Similarly, Moule (1956) reported as birth weight increased from 4.5 to 9 lb, mortality decreased dramatically in lambs.

Mulliniks et al. (2008) and Larson et al. (2009) indicated reduced proportions of steers treated in the feedlot from cows supplemented with protein compared to calves from nonsupplemented dams. Stalker et al. (2006) reported increased proportions of live calves

weaned to dams offered supplement during late gestation; however, there was no difference in the number of treated calves prior to weaning or in the feedlot. Furthermore, Larson et al. (2009) reported no difference in the number of steer calves treated for respiratory disease prior to weaning. Similarly, Funston et al. (2010b) reported no differences in illness in cohort heifers.

Snowder et al. (2006) reported disease incidence is more likely after 5 days on feed and remains high through the first 80 days in the feedlot. Furthermore, steers were more likely to become sick compared to heifers in the feedlot. Post-weaning stress is a factor influencing calf health. As mentioned earlier, Funston et al. (2010b) did not report any differences in heifer calf health. These heifers, unlike their steer cohorts, remained at the ranch post-weaning and were maintained on a forage based diet, likely reducing the amount of stress placed on the animal when compared to their steer cohorts who were transported to the feedlot 2 weeks post-weaning and adapted to a concentrate based diet.

### Summary

Management of maternal diet beginning during early gestation will ensure proper placental programming resulting in adequate nutrient transfer to the fetus. Maternal nutrition later in gestation has been reported to influence fetal organ development, muscle development, postnatal calf performance, carcass characteristics, and reproduction. Although the mechanisms by which placental and fetal programming occur are not clear, managing resources to ensure proper cow nutrient intake during critical points of gestation can improve calf performance and health.

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