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Short-term energy restriction during late gestation of beef cows decreases postweaning calf humoral immune response to vaccination[1]

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ABSTRACT: Our objectives were to evaluate the pre- and postweaning growth and measurements of innate and humoral immune response of beef calves born to cows fed 70 or 100% of NEm requirements during the last 40 d of gestation. On d 0 (approximately 40 d before calving), 30 multiparous Angus cows pregnant to embryo transfer (BW = 631 ± 15 kg; age = 5.2 ± 0.98 yr; BCS = 6.3 ± 0.12) were randomly allocated into 1 of 10 drylot pens (3 cows/pen). Treatments were randomly assigned to pens (5 pens/treatment) and consisted of cows limit-fed (d 0 to calving) isonitrogenous, total-mixed diets formulated to provide 100 (CTRL) or 70% (REST) of daily NEm requirements of a 630-kg beef cow at 8 mo of gestation. Immediately after calving, all cow–calf pairs were combined into a single management group and rotationally grazed on tall fescue pastures (6 pastures; 22 ha/pasture) until weaning (d 266). All calves were assigned to a 40-d preconditioning period in a drylot from d 266 to 306 and vaccinated against infectious bovine rhinotracheitis, bovine viral diarrhea virus (BVDV), *Mannheimia haemolytica*, and *Clostridium* spp. on d 273 and 287. Blood samples from jugular vein were collected from cows on d 0, 17, and 35 and from calves within 12 h of birth and on d 266, 273, 274, 276, 279, and 287. By design, REST cows consumed less ($P \leq 0.002$) total DMI, TDN, and NEm but had similar CP intake ($P = 0.67$), which tended ($P = 0.06$) to increase BW loss from d 0 to calving, than CTRL cows (−1.09 vs. −0.70 ± 0.14 kg/d, respectively). However, gestational NEm intake did not affect ($P \geq 0.30$) plasma concentrations of cortisol, insulin, and glucose during gestation and BCS at calving as well as postcalving pregnancy rate, BW, and BCS change of cows. Calf serum IgG concentrations and plasma concentrations of haptoglobin and cortisol at birth as well as calf pre- and postweaning BW and ADG did not differ ($P \geq 0.15$) between calves born to REST and CTRL cows. However, calf postweaning overall plasma concentrations of cortisol; plasma haptoglobin concentrations on d 274, 276, and 279; and serum BVDV-1a titers on d 306 were less for REST calves than for CTRL calves ($P \leq 0.05$). Hence, a NEm restriction to 70% of daily requirements during the last 40 d of gestation had minimal effects on cow precalving growth and did not affect postcalving cow growth and reproductive performance. However, it decreased postweaning vaccination-induced humoral immunity, inflammatory, and physiological stress responses of calves.

Key words: energy restriction, fetal programming, gestation, immune, preconditioning, vaccination

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INTRODUCTION

The hypothalamic–pituitary–adrenal (**HPA**) axis is activated when the animal must cope with a stressor, resulting in release of cortisol (Sapolsky et al., 2000; Chrousos, 2009). Glucocorticoids mediate the effects of maternal stress on the fetus (Harris and Seckl, 2011) and affect the maturation of the HPA axis, which might cause detrimental effects on

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postnatal offspring health (Wu et al., 2006). For instance, 48 h of maternal nutrient deprivation during the period of maximal fetal brain growth of guinea pigs (d 50 of gestation) decreased fetal plasma glucose concentrations and increased maternal cortisol secretion (Lingas et al., 1999), which, in turn, reached the fetus and modified fetal HPA activity (Go et al., 2001).

Negative energy balance of gestating beef cows is one of the stressors that can be detrimental for placental environment and calf development (Funston et al., 2012) and impact how individuals will respond throughout their lives (Arnott et al., 2012). Calves born to cows that were nutrient restricted during the last trimester of gestation had greater serum cortisol concentrations at birth (Hough et al., 1990) and increased morbidity, mortality, and percentage of calves treated for bovine respiratory disease compared with calves born to cows not nutrient restricted (Corah et al., 1975; Stalker et al., 2006; Larson et al., 2009). However, little is known about the pre- and postweaning growth and immunity of beef calves born to cows exposed to a short-term energy restriction during late pregnancy. We hypothesized that a short-term NEm restriction would increase plasma cortisol concentrations of late-gestating cows, which would impair subsequent calf postweaning growth and postvaccination antibody production. Therefore, our objectives were to evaluate the pre- and postweaning growth and measurements of innate and humoral immune response of beef calves born to cows provided 70 or 100% of daily NEm requirements during the last 40 d of gestation.

Table 1. Average weekly chemical composition of total mixed diets (CTRL and REST[1]) offered to mature cows during the last 40 d of gestation (d 0 to calving) and ground tall fescue hay and concentrate offered to their calves from d 266 to 306 (calf preconditioning phase)[2]

	Cow precalving diet		Calf preconditioning phase	
	CTRL	REST	Tall fescue hay	Concentrate[4]
Item[3]	DM basis			
DM, %	43.5	71.7	91.8	89.0
CP, % of DM	10.5	12.7	11.9	15.9
ADF, % of DM	32.1	41.7	40.1	29.0
NDF, % of DM	50.7	61.8	67.8	50.0
TDN,[5] % of DM	64.7	57.7	55.0	72.0
NEm,[6] Mcal/kg DM	1.39	1.14	1.04	1.65
NEg,[6] Mcal/kg DM	0.81	0.58	0.48	1.04
Ca, % of DM	0.36	0.62	0.33	0.35
P, % of DM	0.27	0.29	0.24	0.58

[1]Diets were formulated to provide 100% of daily CP requirements but were isonitrogenous, total-mixed diets formulated to provide 100 [CTRL] or 70% [REST] of daily NEm requirements of a 630-kg beef cow at 8 mo of gestation. The CTRL and REST diets consisted of 61.9 and 11.8% corn silage and 38.1 and 88.2% ground hay (DM basis), respectively, and were offered at 1.93 and 1.58% of cow BW obtained on d 0 (DM basis), respectively.

[2]Samples of ground tall fescue hay and corn silage were collected individually before the start of the study to formulate diets.

[3]Samples of total mixed diets offered to cows were collected weekly from d 0 to calving, whereas ground tall fescue hay and concentrate offered to calves (postweaning phase) were collected weekly from d 266 to 306 and sent in duplicate to a commercial laboratory for wet chemistry analysis of all nutrients.

[4]Concentrate consisted of 50% soy hulls pellets and 50% corn gluten pellets (DM basis) offered at 1.0% of BW on d 0 (DM basis).

[5]Calculated as described by Weiss et al. (1992).

[6]Calculated using the equations proposed by the NRC (2000).

MATERIALS AND METHODS

The Institutional Animal Care and Use Committee of North Carolina State University (protocol number 15-014-A) approved all procedures for the experiment conducted at the Mountain Research Station (Waynesville, NC; 35.48° N, 82.99° W; elevation 659 m) from January to November 2015.

Animals, Diets, and Sample Collection

Precalving Phase. On d 0 (approximately 40 d before the expected calving date, assuming a 283-d gestation length after the date of embryo transfer), 30 multiparous, nonlactating, spring-calving Angus cows (BW = 631 ± 15 kg; age = 5.2 ± 0.98 yr; BCS = 6.3 ± 0.12, according to Wagner et al., 1988) were randomly selected from a herd of cows pregnant to embryo transfer. Using nonsurgical collection techniques, embryos were collected from mature donor cows that were cohorts of the selected herd and sired by 2 Angus sires. Embryos were kept frozen until the moment of embryo transfer. On d 0, cows were stratified by sire, age, BW, and BCS assessed on d 0 and then randomly allocated into 1 of 10 pens in a drylot feeding facility (n = 3 cows/pen; 15 by 30 m; 150 m^2/cow). Treatments were randomly assigned to pens (n = 5 pens/treatment) and consisted of cows offered isonitrogenous, total-mixed diets formulated to provide 100 (**CTRL**) or 70% (**REST**) of daily NEm requirement of a 630-kg beef cow at 8 mo of gestation (NRC, 2000). On a DM basis, the CTRL diet consisted of 61.9% corn silage and 38.1% ground tall fescue hay (*Lolium arundinaceum*) that was offered at 1.93% of cow BW obtained on d 0, whereas the REST diet consisted of 11.8% corn silage and 88.2% ground tall fescue hay that was offered at 1.58% of cow BW obtained on d 0 (Table 1). Cows were offered diets daily in a covered, concrete, fence-line bunk at 0800 h from d 0 to calving. A complete mineral mix (Tennessee Farmers Cooperative, La Vergne, TN; average composition, DM basis: 14.1% Ca, 0.72% K, 11.5% Mg, 0.76% S, 7.0% Na, 10.8% Cl, 2.0% P, 29 mg/kg Co, 900 mg/kg Cu,

2,130 mg/kg Mn, 20 mg/kg Se, and 1,800 mg/kg Zn) was top-dressed daily at a rate of 0.150 kg/cow from d 0 to calving. Hay was ground through a 2.54-cm screen weekly before feeding.

The daily amount of diet DM offered to cows was adjusted daily to alterations on diet DM concentration. Diet DM offered and refused were obtained daily for each pen by drying samples of diet offered and refused in a forced-air oven at 56°C for 48 h. Daily DMI was determined by subtracting the daily diet DM refused from the daily diet DM offered. Samples of hay and corn silage were collected separately before the start of the study to formulate diets. Samples of total-mixed diets offered to cows were collected weekly from d 0 to calving and then sent in duplicate to a commercial laboratory (Dairy One Forage Laboratory, Ithaca, NY) for wet chemistry analysis of all nutrients (Table 1). Samples were analyzed for concentrations of CP (method 984.13; AOAC, 2006), ADF (method 973.18 modified for use in an Ankom 200 fiber analyzer; Ankom Technology Corp., Fairport, NY; AOAC, 2006), and NDF (Van Soest et al., 1991; modified for use in an Ankom 200 fiber analyzer; Ankom Technology Corp.). Concentrations of TDN were calculated as proposed by Weiss et al. (1992), whereas NEm and NEg were calculated using equations from the NRC (2000).

Individual cow BW and BCS were obtained on d 0 after 12 h of feed and water withdrawal and also immediately after calving and complete placental expulsion. Blood samples (10 mL) were collected from all cows via jugular venipuncture into sodium heparin (158 United States Pharmacopeia units)–containing tubes (Vacutainer; Becton, Dickinson and Company, Franklin Lakes, NJ) for plasma harvest 4 h after diets were offered on d 0, 17, and 35 to determine the plasma concentrations of cortisol, glucose, and insulin.

Preweaning Phase. Immediately after calving, cow–calf pairs were transferred to 1 of 6 tall fescue pastures (22 ha/pasture; 16% CP and 59% TDN, DM basis) with free choice access to water and a complete mineral mix (same as previously described). Cows and calves were managed as a single group and rotated among pastures monthly from calving until weaning (d 266; approximately 227 d of age). No calf was lost at birth, and hence, percentage of live calves at birth was not statistically analyzed. Individual cow BW and BCS as well as calf BW were obtained on d 266 after 12 h of feed and water withdrawal. All male calves were castrated by banding immediately after birth. Cows were placed with 2 Angus bulls from d 121 to 189, whereas pregnancy rate was determined by rectal palpation on d 226 and confirmed at calving.

Postweaning Phase. Immediately after weaning, all steers and heifers were assigned to a 40-d preconditioning period from d 266 to 306. Calves were stratified by treatment and pen distribution that was previously assigned to their dams on d 0 and then randomly allocated into 1 of 10 concrete floor pens in a half-covered drylot feeding facility (3 calves/pen; 18 by 3 m; 18 m^2/calf). This approach was selected because 1) calf gender was not known at the time of treatment assignment and, hence, calf gender was not controlled in the experimental design, which made the test of treatment × gender interaction not possible and (2) percentage of male calves did not differ between treatments at weaning ($P = 0.85$). However, calf gender was included as a covariate in the analyses of all calf variables but removed from the model when $P > 0.10$.

From d 266 to 306, all calves were limit-fed ground tall fescue hay DM at 1.2% of BW and concentrate DM at 1.0% of BW to meet the daily NEm and MP requirements of growing beef steers to achieve 0.90 kg/d of BW gain (NRC, 2000). Concentrate consisted of 50% soy hull pellets and 50% corn gluten pellets (DM basis; Table 1). Hay and concentrate were offered separately in the same concrete, fence-line bunk once daily at 0800 h. Calves consumed the concentrate offered within 30 min of supplementation. Samples of hay offered and refused were collected daily from each pen and dried in a forced-air oven at 56°C for 48 h. Daily hay DMI was determined by subtracting the daily hay DM refused from the daily hay DM offered of each pen. A complete mineral mix (RU-MIN 1600; Southern States, Richmond, VA; average composition, DM basis: 18.2% Ca, 0.72% K, 0.88% Mg, 0.76% S, 7.0% Na, 10.8% Cl, 2.9% P, 29 mg/kg Co, 1,220 mg/kg Cu, 2,130 mg/kg Mn, 29 mg/kg Se, and 2,530 mg/kg Zn) was top-dressed daily over the supplement at a rate of 0.114 kg/calf from d 266 to 306. Samples of hay, concentrate, and mineral mix offered were collected weekly and then sent in duplicate to a commercial laboratory (Dairy One Forage Laboratory) for wet chemistry analysis of all nutrients (Table 1). Hay, concentrate, and total DMI of calves from d 266 to 306 were analyzed as percentage of BW obtained on d 266.

On d 266, all calves were individually treated with doramectin for internal and external parasites (5 mL subcutaneous; Dectomax injectable; Zoetis Inc., Kalamazoo, MI). On d 273, calves were vaccinated against infectious bovine rhinotracheitis virus (**IBRV**), bovine viral diarrhea virus (**BVDV**) types 1a and 2, parainfluenza 3 virus (**PI3**), *Mannheimia haemolytica* (2 mL subcutaneous; Bovi Shield Gold One Shot; Zoetis Inc.), and Clostridium spp. (2 mL subcutaneous; Ultrabac 7; Zoetis Inc.). On d 287, calves received 2-mL subcutaneous boosters of Bovi Shield Gold 5 (Zoetis Inc.) and Ultrabac 7. The vaccination protocol described above was chosen to replicate the protocol used by the local preconditioning alliance (Mountain Cattle Alliance, Canton, NC; Moriel et al., 2015; Artioli et al.,

2015, 2016). The vaccination protocol was initiated 7 d after feedlot entry to avoid the feedlot entry–induced inflammatory response that could interfere with vaccine response (Richeson et al., 2008).

Blood samples (10 mL) were collected from all calves via jugular venipuncture into sodium heparin (158 United States Pharmacopeia units)–containing tubes (Vacutainer; Becton, Dickinson and Company) within 12 h of birth and also on d 266, 273, 274, 276, 279, and 287 to evaluate plasma concentrations of haptoglobin and cortisol. Additional blood samples (10 mL) from jugular vein were collected from all calves into tubes containing no additives (Vacutainer; Becton, Dickinson and Company) for serum harvest to evaluate serum concentrations of IgG within 12 h of birth and on d 266 and 306 to evaluate the vaccination-induced serum antibody titers against IBRV, PI3, and BVDV-1a and -2. Blood samples were immediately placed on ice following collection and then centrifuged at 1,200 × *g* for 25 min at 4°C. Plasma and serum samples were stored frozen at −20°C until later laboratory analysis.

Laboratory Analyses

Plasma concentrations of haptoglobin were determined in duplicate samples using a biochemical assay assessing haptoglobin–hemoglobin complex by the estimation of differences in peroxidase activity (Cooke and Arthington, 2013). Plasma concentrations of cortisol and insulin were determined using a single chemiluminescent enzyme immunoassay (Immulite 1000; Siemens Medical Solutions Diagnostics, Los Angeles, CA). Intra- and interassay CV for haptoglobin assays were 5.3 and 2.2%, respectively, whereas intra-assay CV for the analyses of cortisol and insulin were 1.9 and 0.8%, respectively. Commercial quantitative colorimetric kits were used to determine the plasma concentrations of glucose (G7521; Pointe Scientific, Inc., Canton, MI) and serum concentrations of bovine IgG (E11-118; Bethyl Laboratories, Montgomery, TX; Shoshani et al., 2014). Intra- and interassay CV for glucose assays were 2.5 and 7.7%, respectively, whereas intra-assay of IgG analysis was 3.4%. Serum antibody titers against IBRV, PI3, and BVDV-1a and -2 were determined by the Oklahoma Animal Disease and Diagnostic Laboratory (**OADDL**; Stillwater, OK) using a virus neutralization test (Rosenbaum et al., 1970). Serum titers were reported as the log base 2 of the greatest dilution of serum that provided complete protection of the cells (lowest and greatest tested dilutions were 1:4 and 1:256, respectively; Richeson et al., 2008; Moriel et al., 2015; Artioli et al., 2015). All calves had serum titer values less than 4 on d 266 and, hence, were considered serum negative against IBRV, PI3, and BVDV-1a and -2 according to the OADDL.

Statistical Analyses

All data were analyzed as a completely randomized design using the MIXED procedure of SAS (SAS Inst. Inc., Cary, NC; version 9.3) with Satterthwaite approximation to determine the denominator degrees of freedom for the test of fixed effects. Pen was the experimental unit, whereas animal(pen) and pen(treatment) were included as random effects in all analyses, except for intake data and feed efficiency, which included only pen(treatment) as random effect. Sire was initially included as a block effect in all analyses; however, it was removed from the model as effects of treatment × block and block were not detected ($P \geq 0.37$) for any cow and calf variable analyzed. Cow BW and BCS change, calf plasma data at birth, calf pre- and postweaning ADG, and calf age at weaning were tested for fixed effects of cow gestational diet. Cow daily intake data were pooled by week to simplify data analyses, interpretation, and reporting. Cow daily intake of diet DM, CP, NEm, and TDN were analyzed as repeated measures and tested for fixed effects of cow gestational diet, week of study, and resulting interactions, using pen(treatment) as the subject. Pre- and postcalving BW and BCS of cows, pre- and postweaning calf BW, postweaning calf intake (hay, concentrate, and total DM), and blood measurements of cows (precalving phase) and calves (postweaning phase) were analyzed as repeated measures and tested for fixed effects of cow gestational diet, day of the study, and the resulting interactions. Compound symmetry covariance structure was used for the analyses of cow plasma glucose concentrations. Unstructured covariance structure was used for analyses of postweaning plasma cortisol concentrations of calves, whereas autoregressive 1 was used for all of the remaining analyses of repeated measures. These covariance structures were selected as they generated the lowest Akaike information criterion. Calf gender and cow age were included as covariates in all analyses but were removed from the model when $P > 0.10$. Percentage of male calves at birth was tested for fixed effects of cow gestational diet using GLIMMIX procedure of SAS. All results are reported as least squares means. Data were separated using PDIFF if a significant preliminary F-test was detected. Significance was set at $P \leq 0.05$, and tendencies were noted if $P > 0.05$ and ≤ 0.10.

RESULTS AND DISCUSSION

Precalving Phase

Cows remained on respective treatments for approximately 39.5 d before calving (Table 2). However, a 70% restriction on NEm intake during late gestation did not impact ($P = 0.60$) the number of days that cows remained on respective treatment (Table 2), suggesting

Table 2. Growth and reproductive performance of late gestating beef cows offered isonitrogenous, total-mixed diets formulated to provide 100 (CTRL) or 70% (REST) of daily NEm requirements during the last 40 d of gestation (d 0 to calving; $n = 3$ cows/pen; 5 pens/treatment)

	Treatment[1]			*P*-value	
Item	CTRL	REST	SEM	Treatment	Treatment × day
BW,[2] kg					
d 0	622	639	20.4	0.78	0.54
Calving	587	597	20.5		
Weaning (d 266)	577	598	20.6		
BW change, kg/d					
d 0 to calving[3]	−0.70	−1.09	0.140	0.06	
Calving to weaning[3]	−0.03	0.00	0.026	0.44	
BCS					
d 0	6.55	6.60	0.210	0.92	0.98
Calving	6.55	6.36	0.210		
Weaning (d 266)	6.33	6.46	0.210		
BCS change					
d 0 to calving	0.01	−0.25	0.157	0.30	
Calving to weaning[3]	−0.15	0.19	0.206	0.87	
Days on treatment[4]	41	38	4.2	0.60	
Overall pregnancy,[5] %	74.1	84.6	4.2	0.53	

[1]The CTRL and REST dies were offered at 1.93 and 1.58% of cow BW obtained on d 0 (DM basis), respectively.

[2]Body weight on d 0 and 266 were obtained after 12 h of feed and water withdrawal, whereas BW at calving were obtained after complete placental expulsion (within 12 h of calving).

[3]Covariate-adjusted to cow age ($P \leq 0.006$), although cow age on d 0 did not differ between treatments ($P = 0.44$).

[4]Days on respective treatment (d 0 to calving).

[5]Pregnancy rate was determined by rectal palpation on d 226 and confirmed at calving.

Table 3. Precalving intake and plasma measurements of late gestating beef cows offered isonitrogenous, total-mixed diets formulated to provide 100 (CTRL) or 70% (REST) of daily NEm requirements during the last 40 d of gestation (d 0 to calving; $n = 3$ cows/pen; 5 pens/treatment)

	Treatment[1]			*P*-value	
Item	CTRL	REST	SEM	Treatment	Treatment × time
Cow intake					
Total DMI, kg/d	12.0	10.1	0.23	0.0002	0.64
TDN, kg/d	7.76	5.81	0.153	0.002	0.72
NEm, Mcal/d	16.6	11.5	0.329	0.001	0.67
CP, kg/d	1.28	1.29	0.027	0.67	0.68
Cow plasma measurements[2]					
Glucose,[3] mg/dL	62.2	64.5	2.01	0.43	0.55
Insulin, μIU/mL	2.94	3.01	0.427	0.92	0.65
Cortisol,[4] ng/mL	19.2	20.1	1.69	0.71	0.30

[1]Diets were formulated to provide 100% of daily CP requirements but 70 (REST) or 100% (CTRL) of daily NEm requirements of a 630-kg beef cow at 8 mo of gestation. The CTRL and REST dies were offered at 1.93 and 1.58% of cow BW obtained on d 0 (DM basis), respectively.

[2]Body weight on d 0 and 266 were obtained after 12 h of feed and water withdrawal, whereas BW at calving were obtained after complete placental expulsion (within 12 h of calving).

[3]Overall plasma concentrations of glucose, insulin, and cortisol collected on d 0, 17, and 35.

[4]Means covariate adjusted to cow age ($P \leq 0.05$), although cow age did not differ between treatments ($P = 0.44$).

that a short-term energy restriction did not impact gestation length. Also, a treatment × day of study was not detected for BW and BCS of cows ($P \geq 0.54$; Table 2). By design, REST cows consumed less ($P \leq 0.002$) total DMI, TDN, and NEm (on average, 84.2, 74.9, and 69.3%, respectively, of CTRL cows' intake) but had similar overall CP intake ($P = 0.67$) compared with CTRL cows (Table 3). Consequently, REST cows tended ($P = 0.06$) to lose more BW from d 0 until calving compared with CTRL cows (Table 2). The observed BW loss of REST cows, however, was not sufficient to cause differences on BCS change from d 0 to calving and led to similar BCS at calving compared with CTRL cows. Body weight and BCS change from calving to weaning (d 226) and pregnancy rates did not differ between REST cows and CTRL cows ($P \geq 0.44$; Table 2). It is important to highlight that the number of cows per treatment is relatively low to detect differences on pregnancy rates and also that evaluating the effects of cow gestational diet on subsequent pregnancy rates was not the primary goal of the study. Nonetheless, several reports showed that reproductive performance was not affected, even though cows experienced nutrient restriction. Corah et al. (1975) reported that primiparous cows provided 65% of DE requirements lost 5.8 kg of BW, whereas cows offered 100% of DE requirements gained 36.1 kg for 100 d before calving, but both groups had a similar interval to first estrus and percentage of cows in estrus 40 d after calving. Mature beef cows fed 57% of CP and ME requirements during late gestation were lighter and had less BCS at calving but similar number of days to rebreed compared with cows provided 100% of CP and ME requirements (Hough et al., 1990). In addition, REST and CTRL cows calved in a relatively high BCS (average = 6.46 ± 0.21), and therefore, is not surprising that pregnancy rates of cows did not differ in the current study. These results might also indicate that cows can experience a relatively short period of energy restriction before calving that is not sufficient to affect subsequent reproductive performance of cows and might remain undetectable to beef cattle producers.

Cortisol is a naturally occurring glucocorticoid that regulates metabolic, cardiovascular, immune, and behavioral responses (Smith and Vale, 2006) and was increased in the maternal and fetal plasma of guinea pigs following prenatal stress (Cadet et al., 1986). In addition, glucose is essential for fetal growth (Bell et al., 2005) and its supply to the fetus is modulated by maternal glucose concentration (Baumann et al., 2002),

Table 4. Pre- (birth to d 266) and postweaning growth (d 266 to 306) and blood measurements at birth of calves born to beef cows offered isonitrogenous, total-mixed diets formulated to provide 100 (CTRL) or 70% (REST) of daily NEm requirements during the last 40 d of gestation (d 0 to calving; $n = 3$ calves/pen; 5 pens/treatment)

	Treatment[1]			*P*-value	
Item	CTRL	REST	SEM	Treatment	Treatment × day
Calf BW,[2,3] kg					
Birth	35	37	8.1		0.40
Weaning (d 266)	261	276			
End of preconditioning (d 306)	295	311			
Before weaning (birth to d 266)					
Male calves at birth, %	43.4	47.4	16.3	0.85	
Serum IgG at birth,[3] mg/dL	3,658	3,781	684	0.89	
Plasma cortisol at birth, ng/mL	61.2	59.0	6.77	0.76	
Plasma haptoglobin at birth, mg/mL	0.17	0.23	0.031	0.15	
205-d-adjusted BW,[3,4] kg	243	252	5.2	0.19	
ADG, kg/d	1.01	1.05	0.025	0.24	
Age at weaning, d	225	229	5.6	0.61	
After weaning (d 266 to 306)					
ADG, kg/d	0.80	0.84	0.061	0.59	
Hay DMI, % of BW	1.18	1.16	0.019	0.48	
Concentrate DMI, % of BW	0.94	0.94	0.006	0.80	
Total DMI, % of BW	2.12	2.10	0.020	0.55	
G:F[5]	0.18	0.16	0.012	0.32	

[1]Diets were formulated to provide 100% of daily CP requirements, but 70 (REST) or 100% (CTRL) of daily NEm requirements of a 630-kg beef cow at 8 mo of gestation. The CTRL and REST dies were offered at 1.93 and 1.58% of cow BW obtained on d 0 (DM basis), respectively.

[2]Individual calf BW was obtained immediately after birth and also on d 266 and 306 after 12 h of feed and water withdrawal.

[3]Covariate adjusted to calf gender ($P \leq 0.07$), although percentage of male calves at birth did not differ between treatments ($P = 0.85$).

[4]Calculated according to the Beef Improvement Federation (2010).

[5]Calculated using total BW gain divided by total DMI from d 266 to 306.

whereas stress on the dam can reduce fetal growth and birth BW and was associated with greater risk of neonatal mortality and morbidity (Vonnahme et al., 2013). For instance, Lay et al. (1997) observed that exposing pregnant Brahman cows to repeated transport on d 60, 80, 100, 120, and 140 of gestation increased the offspring stress-induced cortisol response to restraint at 10 and 150 d of age. Hence, we hypothesized that a short-term nutrient restriction during the last 40 d of gestation would decrease maternal plasma concentrations of glucose and insulin and increase maternal plasma cortisol concentrations, which would be detrimental for pre- and postnatal calf development.

Effects of treatment × day of study and treatment were not detected ($P \geq 0.43$) for plasma concentrations of glucose and insulin of REST and CTRL cows (Table 3). This outcome was unexpected because blood samples were collected at the peak of release of ruminal fermentation products and insulin (Moriel et al., 2012) and also because insulin and glucose are both directly influenced by nutrient intake (Vizcarra et al., 1998). However, our results indicate that REST cows were capable of maintaining their plasma concentrations of glucose and insulin at the expense of other nutrients (Harmon, 1992). Contrary to our hypothesis, effects of treatment and treatment × day of study were not detected for plasma cortisol concentrations of cows ($P \geq 0.30$; Table 3). In guinea pigs, a 40% reduction on maternal feed consumption during the last 2 trimesters of gestation increased maternal and fetal serum concentrations of cortisol (Dwyer and Stickland, 1992), whereas a 50% reduction on global nutrient intake decreased maternal plasma cortisol concentrations on d 30 but not on d 0 and 65 of gestation compared with ewes fed 100% of nutrient requirements (Cleal et al., 2007). Maternal plasma cortisol concentrations were increased after a 50% reduction on global nutrient intake applied during the first 30 d but not from d 31 to 100 of gestation compared with ewes fed 100% of nutrient requirements (Chadio et al., 2007). Hence, the outcome of gestational nutrient restriction on maternal plasma concentrations of cortisol is dependent on animal specie and stage of gestation and might explain the lack of detectable differences in plasma cortisol concentrations between REST cows and CTRL cows during late gestation.

Pre- and Postweaning Phases

Few studies have compared the impact of prenatal stress on HPA activity in male and female offspring

exposed to identical prenatal protocols, and results have been variable (McCormick et al., 1995; Koehl et al., 1999; Littlejohn et al., 2016). In rats, basal plasma ACTH concentrations and pituitary–adrenocortical responsiveness to stress were increased in adult female offspring but reduced in male offspring born to prenatally stressed dams (McCormick et al., 1995). As previously stated, calf gender was not known at the time of treatment assignment in the current study, and hence, calf gender was not controlled in the experimental design, which made the test of treatment × gender interaction not possible. However, calf gender was included as a covariate in the analyses of all calf variables. Only calf BW, serum IgG at birth (Table 4), and serum BVDV-1a titers (Table 5) were covariate adjusted to calf gender ($P \leq 0.07$). However, percentage of male calves at birth did not differ between treatments ($P = 0.85$; Table 4), and therefore, treatment differences that will be described herein were not associated with differences on calf gender.

Effects of treatment and treatment × day of the study were not detected for calf pre- and postweaning BW ($P \geq 0.12$; Table 4). These responses on calf BW were not associated with calf age, as calf 205-d-adjusted BW did not differ between treatments ($P = 0.19$; Table 4). Calves born to REST cows and calves born to CTRL cows had similar preweaning ADG ($P = 0.24$; Table 4). During the preconditioning phase (d 266 to 306), calves were limit fed the same amount of hay and concentrate DM (% of BW) to avoid any potential differences in growth performance caused by different total DMI. As expected, hay and concentrate intake and total DMI (% of BW) did not differ between treatments ($P \geq 0.48$; Table 4). However, ADG and G:F from d 266 to 306 also did not differ ($P \geq 0.32$; Table 4) between calves born to REST cows vs. calves born to CTRL cows.

Energy deficiency (70% of requirements) in primiparous beef cows during the last 100 d of pregnancy decreased calf BW at birth (29 vs. 31 kg, respectively) and at weaning (148 vs. 161 kg, respectively) compared with calves born to dams fed 100% of requirements (Corah et al., 1975). In contrast, calf birth (39 vs. 39 kg, respectively) and weaning BW (240 vs. 243 kg, respectively) were not impacted when dams were fed 57 or 100% of NRC protein and energy requirements during the last 90 d of gestation (Hough et al., 1990). In the current study, the lack of treatment effects on calf preweaning growth might be associated with a variation on preweaning calf BW within each treatment that was greater than the one used in the priori sample calculation to determine the number of replicates per treatment. Nevertheless, calf BW at birth and weaning were numerically greater for calves born to REST cows than for calves born to CTRL cows, which is contrary to our hypothesis and studies described above (Corah et al., 1975; Hough et al., 1990).

Table 5. Postweaning (d 266 to 306) plasma concentrations of cortisol and haptoglobin, and serum titers against bovine viral diarrhea virus (BVDV) types 1a and 2, infectious bovine rhinotracheitis virus (IBRV), and parainfluenza 3 virus (PI3) of calves born to cows offered isonitrogenous, total-mixed diets formulated to provide 100 (CTRL) or 70% (REST) of daily NEm requirements during the last 40 d of gestation (d 0 to calving; $n = 3$ calves/pen; 5 pens/treatment)

	Treatment[1]			*P*-value
Item	CTRL	REST	SEM	Treatment
Plasma measurement[2]				
Cortisol, ng/mL	17.5	13.7	1.53	0.05
Haptoglobin, mg/mL	0.53	0.42	0.043	0.10
Serum titers on d 306,[3] $\log_2$				
BVDV-1a[4]	6.36	5.15	0.463	0.05
BVDV-2	7.49	7.59	0.136	0.58
IBRV	2.37	2.15	0.363	0.66
PI3	6.58	7.23	0.314	0.14

[1]Calves were allocated to drylot pens on d 266 (same pen distribution assigned to cows on d 0) and limit fed ground fescue hay DM at 1.2% of BW and concentrate DM at 1.0% of BW from d 266 to 306.

[2]Overall plasma concentrations of cortisol and haptoglobin collected on d 266, 273, 274, 276, 279, and 287.

[3]All calves were serum negative (titers < 4) against BVDV-1a, BVDV-2, IBRV and PI3 measured on d 266. Hence, treatment × day effects were not tested for serum antibody titers.

[4]Covariate adjusted to calf gender ($P = 0.04$), although percentage of male calves at birth did not differ between treatments ($P = 0.85$).

In the current study, cows were provided their respective treatment for an average of 40 d before calving, whereas in the studies described above, cows were nutrient restricted for 90 to 100 d before calving. Outcomes of fetal programming on offspring performance are highly variable based on available studies (Funston et al., 2012) and several pre- and postnatal factors could interact with gestational treatments and impact these outcomes (as will be described below). Therefore, it is possible that not only duration and magnitude but also timing of nutrient restriction might result in different consequences on calf growth performance, which reinforces the need for additional fetal programming studies in beef cattle.

Transfer of immunoglobulins from maternal serum to colostrum in cattle typically begins 4 wk before parturition and reaches maximum rate a few days before parturition (Olson et al., 1981). Also, there is a linear relationship between calf colostral IgG intake and serum IgG concentrations (Hopkins and Quigley, 1997). Serum IgG concentration of calves within 12 h after birth did not differ between calves born to REST cows and calves born to CTRL cows ($P = 0.89$; Table 4) and were above the minimum threshold considered to be adequate passive immunity transfer (>1,600 mg/dL; Wittum and Perino, 1995). Hough et al. (1990) re-

ported similar IgG concentrations in the colostrum of beef cows fed diets at 100 or 57% of prepartum ME requirements. Calves born to dams that received protein supplementation and gained BW during the last trimester of gestation had serum IgG concentrations at birth similar to calves born to cows that were not supplemented and that lost BW during late gestation (Bohnert et al., 2013). Therefore, calves in the current study were able to achieve the necessary plasma IgG concentrations for adequate immunity regardless of diet provided to cows during the last 40 d of gestation.

Haptoglobin and cortisol are released after an acute-phase response (Moriel and Arthington, 2013). Haptoglobin prevents Fe utilization for bacterial growth (Wassell, 2000) and may be used as an indicator of inflammatory conditions in cattle when plasma concentrations are ≥0.11 mg/mL (Tourlomoussis et al., 2004). During periparturient processes, serum cortisol concentrations of calves typically peak at birth and then gradually decrease for 7 d (Mastorakos and Ilias, 2003; Burdick et al., 2009). In the present study, plasma concentrations of cortisol at birth were on average 3.85-fold greater than the overall concentrations observed during the preconditioning phase (Tables 4 and 5), but they did not differ (*P ≥ 0.15;* Table 4) between calves born to REST cows and calves born to CTRL cows. Also, a short-term energy restriction during the last 40 d of gestation did not exacerbate the inflammatory response experienced by calves at birth. In contrast, serum cortisol concentrations at birth were greater for beef calves born to dams fed 57 vs. 100% of CP and ME requirements during the last 90 d of gestation (Hough et al., 1990). Therefore, it is possible that the duration of energy restriction used herein was not sufficient to induce differences in plasma concentrations of haptoglobin and cortisol at birth. Although cortisol is important for neonatal organ development (Owen et al., 2005), cortisol may also stimulate an acute-phase response (Cooke and Bohnert, 2011) that impairs the innate and humoral immune response (Dai and McMurray, 1998; Salak-Johnson and McGlone, 2007). As previously described, prenatal physiological or psychological stress permanently altered the offspring capacity to cope with stressors (Arnott et al., 2012). Hence, it was our interest to also evaluate calf innate and humoral immune responses to a preconditioning and vaccination protocols after weaning.

Weaning, feedlot entry, and vaccination often elicit an acute phase response, leading to increased concentrations of cortisol and haptoglobin (Arthington et al., 2013; Moriel and Arthington, 2013). In agreement, effects of day of study were detected for plasma concentrations of cortisol (*P* = 0.05), which increased from d 266 to 283 (12.9, 13.2, 15.9, 15.9, 17.5, and 18.2 ± 2.17 ng/mL for d

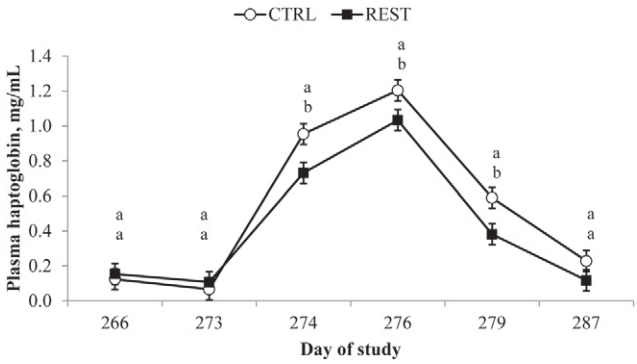

Figure 1. Postweaning plasma haptoglobin concentrations (d 226 to 287) of calves born to beef cows offered isonitrogenous, total-mixed diets formulated to provide 100 (CTRL) or 70% (REST) of daily NEm requirements during the last 40 d of gestation (d 0 to calving; *n* = 3 calves/pen; 5 pens/treatment). Calves were weaned on d 266 and assigned to a 40-d preconditioning period with vaccination against bovine respiratory disease–associated pathogens on d 273 and 287. Effect of treatment × day of study was detected (*P* = 0.05) for plasma concentrations of haptoglobin from d 266 to 287. [a,b]Within day, means without a common superscript differ (*P* ≤ 0.05).

266, 273, 274, 276, 279, and 287, respectively). Effects of treatment × day of study were detected for plasma concentrations of haptoglobin (*P* = 0.05; Fig. 1) but not for plasma cortisol concentrations (*P* = 0.45). Calves born to REST cows had less (*P* ≤ 0.04) plasma concentrations of haptoglobin on d 274, 276, and 279 than calves born to CTRL cows (Fig. 1). However, overall plasma cortisol concentrations were less (*P* = 0.05) for calves born to REST cows than for calves born to CTRL cows (Table 5). Timing of maternal exposure to glucocorticoid during gestation affected the HPA outcome in pigs (Kranendonk et al., 2006). Offspring whose mothers were treated with hydrocortisone in mid gestation exhibited elevated basal salivary concentrations of cortisol at 6 wk of age, whereas those exposed in early and late gestation exhibited normal basal cortisol but lessened responses to an ACTH challenge. Therefore, the discrepancy between our results and others might also be related to timing and duration of undernutrition applied (last 40 vs. 90–100 d of gestation). Furthermore, the outcome of a prenatal synthetic glucocorticoid exposure on HPA function varies with the age of offspring. At 2 mo of age, the corticotropin-releasing hormone-induced plasma concentrations of cortisol were increased in lambs born to ewes that were provided 50% of global nutrient intake during the first 30 d compared with ewes provided 100% of nutrient requirement throughout gestation and ewes provided 50% of nutrient intake from d 31 to 100 of gestation (Chadio et al., 2007). However, plasma cortisol concentrations of lambs following a similar corticotropin-releasing hormone challenge did not differ among treatments at 5.5 and 10 mo of age (Chadio et al., 2007). In agreement, a single maternal injection of betamethasone at d 104 of gestation had little effect on HPA function in offspring at 6 mo of age but increased offspring basal and stimulated

plasma cortisol concentrations at 1 yr of age (Sloboda et al., 2002). Taken together, timing of nutrient restriction and calf age at the time of stress may explain why, in the current study, a short-term energy restriction during late gestation decreased calf plasma concentrations of cortisol and haptoglobin after weaning but not at birth.

Neutralizing serum antibody titers may be used as an indicator of immune protection, disease prevention, and vaccine efficacy in calves (Howard et al., 1989; Bolin and Ridpath, 1995). The ability of an animal to respond to vaccination differs from animal to animal and depends on environmental and genetic factors, maternal antibody concentrations (Downey et al., 2013), calf age (Kirkpatrick et al., 2008), timing of vaccination after feedlot entry (Richeson et al., 2008), MP supply (Moriel et al., 2015), and also frequency of supplementation (Artioli et al., 2015, 2016). In humans, prenatal undernutrition impaired cell-mediated immunity and antibody responses to vaccination (Chandra, 1981). In the current study, all calves were serum negative (titers < 4) for antibody titers against BVDV-1a, BVDV-2, IBRV, and PI3 measured on d 266. Hence, treatment × day effects were not tested for serum antibody titers. Serum titers against BVDV-2, IBRV, and PI3 on d 306 did not differ between treatments ($P \geq 0.14$), but calves born to REST cows had less ($P = 0.05$; Table 5) serum BVDV-1a titers on d 306 than calves born to CTRL cows, which is in agreement with our hypothesis. The results on serum BVDV-1a titers and plasma concentrations of cortisol and haptoglobin reported in the current study indicate that even a short-term NEm restriction to 70% of daily prepartum requirements during late gestation might cause immunosuppression effects in the offspring. It remains unknown if the interaction between innate and humoral immunity was affected and also the duration of such immunosuppression effects in REST calves. Consequently, further studies are warranted to determine whether the effects of gestational diet on immune response of REST calves were transient or permanent. Nonetheless, our results could also explain the greater calf morbidity, mortality, and percentage of calves treated for bovine respiratory disease after cows were nutrient restricted during late gestation (Corah et al., 1975; Stalker et al., 2006; Larson et al., 2009).

In summary, NEm restriction to 70% of daily requirements during the last 40 d of gestation decreased precalving BW gain, but it did not affect precalving plasma concentrations of glucose, insulin, and cortisol of cows. Also, this short-term energy restriction did not affect calf pre- and postweaning growth, serum IgG concentrations, and plasma concentrations of haptoglobin and cortisol at birth. However, calves born to energy-restricted cows had less postvaccination plasma concentrations of cortisol and haptoglobin and serum titers against BVDV-1a than calves born to unrestricted cows. Therefore, a short-term energy restriction during the last 40 d of gestation suppresses vaccination-induced humoral immunity and physiological stress responses of beef calves, which might be detrimental to calf postweaning susceptibility to bovine respiratory disease.

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