Effects of feeding a high- or moderate-starch prepartum diet to cows on newborn dairy heifer calf responses to intravenous glucose tolerance tests early in life

J. Haisan,¹ Y. Inabu,² W. Shi,¹ and M. Oba^{1*}

¹Department of Agricultural Food and Nutritional Science, University of Alberta, Edmonton T6G 2P5, Canada

²The Research Center for Animal Science, Graduate School of Biosphere Science, Hiroshima University, Higashi-Hiroshima, Japan 739-8528

ABSTRACT

The objective of this study was to evaluate the effect of feeding a prepartum diet with a high or moderate starch content on growth and insulin sensitivity of female offspring early in life. Thirty-eight Holstein heifer calves were born to dams fed either a high-starch (26% starch on a DM basis, HI; $n = 20$) or moderate-starch (14% starch on a DM basis, MOD; $n = 18$) prepartum diet commencing at 28 ± 3 d before expected parturition date. Following birth, all calves were housed individually and fed three 2-L meals of colostrum within the first 24 h of life and offered 10 L/d of milk replacer (26% CP, 18% fat, mixed to 130 g/L). Body weight of calves was measured at birth and on d 2 (after colostrum feeding but before milk feeding), 10 ± 2 , and 20 ± 2 . A glucose tolerance test was performed at a minimum of 6 h after their last colostrum or milk meal to evaluate insulin sensitivity on d 2, 10 ± 2 and 20 ± 2 . Body weight did not differ throughout between HI and MOD calves; however, calves born to primiparous dams were smaller compared with those born to multiparous dams. Glucose or insulin concentrations were not different before the glucose tolerance test. Following the glucose tolerance test, maximum glucose concentrations were not different between treatments at any time point. However, HI calves had greater insulin area under the curve, and HI calves had greater maximum insulin concentrations on d 2. Glucose or insulin clearance rates were not different nor was the calculated insulin sensitivity index between treatments. These findings suggest that feeding a HI prepartum diet may reduce some insulin sensitivity indicators of female offspring early in life.

Key words: prepartum diet, calf, insulin sensitivity

INTRODUCTION

The evidence is increasing that maternal nutrition has lasting effects on phenotypic development of offspring, conducted using laboratory models such as rats and mice (Nivoit et al., 2009; Ashino et al., 2012) and domestic mammals such as sheep and cattle. Research has been conducted using sheep or beef cattle using nutrient restriction models at different stages of gestation to evaluate the long-term effects on offspring growth and development (Funston et al., 2010; Chavatte-Palmer et al., 2018). However, little work has been conducted to evaluate the effects of prepartum diets fed to dairy cows.

In dairy cattle production systems, it is common to feed a prepartum diet commencing at 3 to 4 wk before expected parturition date. These diets are typically characterized as being high- or controlled-energy diets. High-energy diets have previously been recommended to increase DMI and milk production in early lactation (McNamara et al., 2003; Janovick and Drackley, 2010). However, recent research has shown that controlled-energy prepartum diets, typically characterized as being high in fiber and low in starch (Mann et al., 2015), maintain DMI around parturition and metabolic status postpartum (Janovick et al., 2011; Vickers et al., 2013).

These feeding strategies may result in altering the energy status of the dam; for example, feeding high-energy diets prepartum is associated with an increase in glucose and insulin concentrations of the cow (Cardoso et al., 2013). Feeding a diet in excess of energy requirements to sheep and beef cattle has been shown to result in offspring exhibiting increased short- and long-term insulin sensitivity (Long et al., 2010a,b). A growing amount of research is being conducted in beef cattle determining the effects of maternal nutrition, throughout various periods of gestation, on offspring growth and development (Hough et al., 1990; Funston et al., 2010). However, little information exists on the effects that the prepartum diet of dairy cows may have on offspring growth and insulin sensitivity.

Received December 29, 2018.

Accepted June 20, 2019.

*Corresponding author: moba@ualberta.ca

Therefore, the objective of this experiment was to determine whether differences in starch content of the prepartum diet could affect early life offspring growth and insulin sensitivity. The hypothesis was that providing a high-starch prepartum diet would reduce sensitivity to insulin in newborn calves.

MATERIALS AND METHODS

All procedures were preapproved by the Animal Care and Use Committee for Livestock at the University of Alberta (AUP #2342). All calves used in the study were born at the University of Alberta Dairy Research and Technology Centre between August 2017 and April 2018.

Dam Experimental Design, Treatments, and Sample Collection

Forty primi- and multiparous cows predetermined to be having female calves via ultrasonography at 60 to 90 d following insemination were enrolled in the study at 28 ± 3 d before expected parturition date. Cows were fed a prepartum diet formulated to meet the requirements of a dry cow carrying a calf at 265 d in gestation (NRC, 2001) containing either a high (26%; **HI**, $n = 20$) or moderate (14%; **MOD**, $n = 20$) starch content on a DM basis (Table 1). Treatment assignment of dams was balanced for BCS and parity of cows at enrollment. All cows were housed in a tiestall barn until approximately 2 d before calving, when they were moved to an individual maternity pen, where they remained until parturition. The diet was fed as a TMR, *ad libitum*, once daily at 0800 h, and cows had free access to water.

Daily feed intake was monitored for individual cows, and the amount of TMR fed was adjusted daily to maintain 5% refusals. Dietary ingredients were sampled weekly and dried for 72 h at 55°C in a forced-air oven to determine DM content, and diets were adjusted weekly to maintain the difference in dietary starch content between the 2 treatments. A subsample of the dried ingredients was kept and composited by month to determine chemical composition of the diet.

At enrollment and 12 ± 2 d before expected parturition date, 2 blood samples were collected before feeding into a sodium heparin or serum Vacutainer (BD Vacutainer, Franklin Lakes, NJ). The sodium heparin Vacutainer was immediately placed on ice until centrifugation at $3,000 \times g$ for 20 min at 4°C, and plasma was stored at -20°C until analysis. The serum Vacutainer was left at room temperature for 1 h before centrifugation at $3,000 \times g$ for 20 min at 4°C, and serum was stored at -20°C until analysis. Dam BCS was measured within 3 d fol-

lowing parturition. For a calf to be used for postnatal sampling, the dam must have been on the prepartum diet a minimum of 14 d, and blood samples needed to be collected on d 12 ± 2 before expected parturition.

Offspring Experimental Design and Sample Collection

All calves were removed from the dam within 2 h of birth and fed 2 L of re-constituted powdered colostrum (HeadStart, Saskatoon Colostrum Company Ltd., Saskatoon, SK, Canada) delivering 120 g of IgG followed by 2 meals of pooled, pasteurized colostrum within the first 24 h of life. Colostrum was tested with a digital Brix refractometer and required a reading of 22 or greater, indicating an immunoglobulin content of 50 mg/L or greater (Bielmann et al., 2010). Pooled colostrum from one batch was pasteurized at 60°C for 60 min and stored at -20°C until use. Calves were then offered 10 L/d of a milk replacer fed at 130 g/L (26% CP, 18% fat; Grober Excel with Pro-Gro Calf Milk Replacer, Grober Nutrition, Cambridge, ON, Canada). Two calves were removed from the study because one was found to be nursing following birth, and the other calf did not consume more than 6 L/d of milk during the study period. Therefore, the data presented are based on final numbers of $n = 18$ for MOD (5 born to primiparous dams) and $n = 20$ for HI (8 born to primiparous dams).

Table 1. Ingredient and nutrient composition of the high-starch (HI) and moderate-starch (MOD) prepartum diets fed to cows from 28 d before expected parturition until parturition

Item	HI	MOD
Ingredient, % of DM		
Barley silage	56.6	56.9
Straw	4.4	23.6
Barley grain	22.1	—
Canola meal	1.8	6.6
Malt sprouts	7.0	7.0
Soy hulls	2.6	0.9
Urea	0.5	0.5
Mill run	1.7	1.8
Canola oil	0.4	0.4
Mineral and vitamin mix ¹	2.9	2.4
Nutrient content		
DM, %	42.1	42.8
CP, % of DM	14.6	15.0
ADF, % of DM	23.3	31.5
NDF, % of DM	37.8	47.7
Starch, % of DM	26.1	14.0
NFC, % of DM	39.4	28.1
DCAD, mEq/kg	28	30
NE _L , Mcal/kg of DM	1.63	1.54

¹Contained 10.9 kIU/kg of vitamin A, 1.7 kIU/kg of vitamin D, 4.3 kIU/kg of vitamin E, 0.52 mg/kg of Co, 5.51 mg/kg of Cu, 22.6 mg/kg of Mn, 29.3 mg/kg of Zn, and 0.20 mg/kg of Se.

Calves were housed in individual pens and offered milk replacer using the Calf Rail (Foerster-Technik, Engen, Germany) connected to an automated calf feeder (CF1000+, DeLaval Canada, ON, Canada). Calves were offered 2-L milk meals 5 times per day, and actual daily intake was recorded automatically via the automated calf feeder. Water was provided starting on d 3, and starter was not offered for the duration of the study. Health events were recorded daily as required.

Body weight was recorded at birth and d 2, 10 (± 2 d), and 20 (± 2 d) of life. On d 2 after colostrum feeding but before the first milk feeding, d 10 ± 2 , and d 20 ± 2 of life (herein referred to d 2, 10, and 20, respectively), an intravenous glucose tolerance test (GTT) was executed after a minimum 6-h fast from the last colostrum or milk meal. A jugular catheter (Surflash 16 gauge $\times$ 2.5 inches, Terumo, Burlington, ON, Canada) was inserted 30 min before the GTT to facilitate frequent blood sampling and remained in the calf for the duration of GTT sampling. The GTT involved an intravenous infusion of glucose occurring over no more than 30 s (50% dextrose solution, DM Vet, Coaticook, QC, Canada) at a dose of 180 mg/kg of BW via the jugular catheter. The dose was based on previous studies reported in calves (Bossaert et al., 2009; Yunta et al., 2015).

Blood samples were collected via a jugular catheter at -5 , 0, 3, 6, 9, 12, 18, 24, 30, 45, 60, and 90 min relative to the glucose infusion. Catheters were flushed with 1.5 mL of saline before and after sample collection during frequent sampling and flushed with 1.5 mL of heparinized saline (2% solution) when duration between samples was more than 6 min. A 0.5-mL waste sample was collected and discarded before blood samples were collected using 5-mL syringes and then placed into a sodium heparin Vacutainer (BD Vacutainer). Following collection, samples were immediately placed on ice before centrifugation at $3,000 \times g$ for 20 min at 4°C ; harvested plasma samples were stored at -20°C until analysis. At time point -5 min, an additional 5-mL sample was collected and placed into a serum Vacutainer (BD Vacutainer) and left at room temperature for 2 h before centrifugation at $3,000 \times g$ for 20 min at 4°C ; harvested serum was stored at -20°C until analysis.

Sample Analyses

Dam and calf plasma samples were analyzed for concentrations of glucose and insulin, and serum samples were analyzed for IGF-1. Plasma glucose concentration was determined using a glucose oxidase/peroxidase enzyme dianisidine dihydrochloride (Sigma-Aldrich), and absorbance at 450 nm was determined using a SpectraMax 190 plate reader (Molecular Devices Corp.,

Sunnyvale, CA). Plasma insulin concentration was determined using a solid-phase competition immunoassay with Eu-labeled bovine insulin and polystyrene microtiter strips coated with anti-guinea pig γ -globin (Takahashi et al., 2006; Inabu et al., 2017). Serum samples were analyzed for IGF-1 at Prairie Diagnostic Services (University of Saskatchewan, Saskatoon, SK, Canada) using a solid-phase, enzyme labeled chemiluminescent immunometric assay using a commercially available kit (Immulite 1000 analyzer, Siemens, Oakville, ON, Canada).

Calculations and Statistical Analysis

For glucose and insulin during the GTT, basal concentration, time to reach maximum concentration (**Tmax**), maximum concentration (**Cmax**), the change in concentration (**delta**), and ratio of delta-to-Tmax were calculated from the raw data. The positive incremental area under the curve (**AUC**) for glucose and insulin was evaluated using the trapezoidal rule and was calculated over the 90-min GTT.

The clearance rate of glucose and insulin was calculated using

$$\text{Clearance rate (\%/min)} = \frac{\{(\ln[t_a] - \ln[t_b]) / (t_b - t_a)\} \times 100,$$

where $[t_a]$ and $[t_b]$ are the concentration of glucose or insulin at time t_a or t_b , respectively (Pires et al., 2007).

Insulin sensitivity was estimated using the simplified model described by Christoffersen et al. (2009):

$$\text{Insulin sensitivity (mg/min} \times \text{ng/mL)} = (30 \times K_G) \times (\text{AUC}_{\text{ins}})^{-1},$$

where K_G is the negative slope of the linear regression of the logarithmic of glucose versus time in the 25-min interval from 5 to 30 min and AUC_{ins} is the AUC of insulin calculated using the trapezoidal rule from 0 to 30 min.

Dam data, calf BW, and ADG were analyzed using the FIT model of JMP (version 14; SAS Institute Inc., Cary, NC) with the following model:

$$Y_{ij} = \mu + T_i + P_j + TP_{ij} + e_{ij},$$

where Y_{ij} is the dependent variable, μ is the overall mean, T_i is the effect of dam treatment, P_j is the effect of dam parity (primi- vs. multiparous), TP_{ij} the effect of dam parity by treatment interaction, and e_{ij} is the residual.

Table 2. The effects of feeding a prepartum diet containing a high (HI) or moderate (MOD) starch content on dam body condition change from enrollment to parturition and serum IGF-1, plasma insulin, and glucose concentrations at enrollment and 12 ± 2 d before the expected calving date

Item	Primiparous		Multiparous		SEM	<i>P</i> -value ¹		
	HI	MOD	HI	MOD		Trt	Parity	Trt × parity
BCS change	−0.2	−0.1	−0.2	−0.03	0.11	0.50	0.39	0.44
IGF-1, ng/mL								
Enrollment	127	161	107	112	13.6	0.13	0.01	0.27
12 d before calving	178	166	120	92.5	18.6	0.25	<0.01	0.67
Insulin, ng/mL								
Enrollment	1.48	1.80	1.83	1.56	0.205	0.91	0.82	0.20
12 d before calving	1.75	1.34	1.78	1.44	0.165	0.04	0.68	0.83
Glucose, mg/dL								
Enrollment	69.2	70.3	69.8	67.0	3.35	0.79	0.68	0.56
12 d before calving	66.2 ^{ab}	66.9 ^{ab}	71.2 ^a	64.1 ^b	2.65	0.50	0.87	0.04

^{a,b}Least squares means within a row with different superscripts differ ($P < 0.05$).

¹Trt = dam dietary treatment, Parity = dam parity.

Milk intake and glucose and insulin concentrations over the GTT were initially analyzed to include the effect of dam treatment, dam parity, and sampling time as a repeated measure. Dam parity nor the parity by treatment interaction was not significant for milk intake or concentrations over the GTT; therefore, they were removed from the model and data were analyzed using the MIXED procedure of SAS 9.4 (SAS Institute Inc.) with the following model:

$$Y_{ij} = \mu + C + T_i + S_j + TS_{ij} + e_{ij},$$

where Y_{ij} is the dependent variable, μ is the overall mean, C is the random effect of calves, T_i is the effect of dam treatment, S_j is the fixed effect of sampling time used as a repeated measure, TS_{ij} is the effect of dam treatment by sampling time interaction, and e_{ij} is the residual. Covariance error structures were tested to determine which yielded lowest Akaike and Bayesian information criterion values. The covariance structure that best suited the data was compound symmetry. When effect of sampling time or treatment by sampling time interaction was significant, least squares means were separated using the PDIF procedure of SAS.

Significance was declared when $P < 0.05$, and tendencies were discussed when $P < 0.10$. Pearson correlation coefficients were determined using the MULTIVARIATE method of JMP (SAS Institute Inc.).

RESULTS

Dam Duration of Feeding, BCS, and Blood Metabolites

Actual days fed the prepartum diet did not differ between treatments (mean ± SD for HI: 24 ± 3.2 d and

MOD: 25 ± 4.1 d), and BCS change from enrollment until calving was not different between HI and MOD cows (Table 2).

Before enrollment and 12 ± 2 d before calving, serum IGF-1 concentration did not differ between treatments; however, primiparous cows had greater IGF-1 than multiparous cows (Table 2). At enrollment, insulin concentrations did not differ; however, at 12 ± 2 d before expected calving date, cows fed HI had greater insulin concentrations as compared with MOD [1.76 vs. 1.40 ± 0.115 (SEM) ng/mL; $P = 0.04$]. Treatment had no effects on plasma glucose concentrations at enrollment (Table 2). However, a treatment × parity interaction existed at 12 ± 2 d before expected calving date ($P = 0.04$) whereby multiparous cows fed HI had greater glucose concentrations compared with multiparous cows fed MOD (Table 2).

Calf Intake, Health, and BW

All calves consumed all colostrum fed, and milk replacer intake did not differ between treatments (Figure 1). One calf in the MOD group was treated for diarrhea at d 7 of life with a single injection of Metacam (1.25 mL/50 kg, Boehringer Ingelheim, Burlington, ON, Canada) and two 2-L feedings of electrolyte solution (92.5 g/L of Calf Lyte II HE, Vetoquinol, Lavaltrie, QC, Canada). However, she recovered and resumed milk intake; therefore, sampling was not affected.

Birth BW nor BW at any measured time point did not differ between HI and MOD calves ($P = 0.69$; Table 3). The HI calves had lower gain as compared with MOD in the period between d 2 and 10 (0.67 vs. 0.89 kg/d; $P = 0.03$, Table 3), and no difference in ADG was observed between d 10 and 20.

Figure 1. Milk intake of calves born to dams fed a high-starch (solid circle) or moderate-starch (open circle) diet prepartum. Calves were fed colostrum over the first 24 h of life and then offered 10 L/d of milk replacer. Data are LSM $\pm$ SEM. Trt = dam dietary treatment. Trt, $P = 0.58$; Time, $P = 0.001$; Trt $\times$ Time, $P = 0.35$.

Basal Concentrations of IGF-1, Plasma Glucose, and Insulin in Calves

Serum IGF-1 concentrations nor basal plasma glucose and insulin concentrations measured before the GTT differed at any time point (Table 4). Concentrations of IGF-1 and glucose increased between d 2 and 10 regardless of treatment.

GTT

Results of the GTT are presented in Table 4 and Figure 2. Plasma glucose concentrations reached maximum concentrations within 3 to 6 min after the infu-

sion. Maximum concentration reached did not differ between treatments ($P = 0.16$); however, concentrations increased with age (Table 4). Glucose AUC was lower for HI calves as compared with MOD calves ($P = 0.05$) and, overall, increased with age. Glucose clearance rate was not affected by treatment. Insulin Tmax occurred within 9 to 12 min after the glucose infusion and was not affected by treatment. Significant treatment $\times$ day interactions were detected for insulin Cmax ($P = 0.04$) and insulin delta ($P = 0.03$). Insulin Cmax was greater by 70% for HI compared with MOD at d 2 (11.1 vs. 6.55 ng/mL; $P < 0.05$) but not at d 10 or 20. Similarly, insulin delta was greater for HI compared with MOD at d 2 (8.80 vs. 4.35 mg/dL; $P = 0.05$), with no difference

Table 3. The effect of feeding a prepartum diet containing a high (HI) or moderate (MOD) starch content to dairy cows on early life growth of female offspring

Item	Primiparous		Multiparous		SEM	P -value ¹		
	HI	MOD	HI	MOD		Trt	Parity	Trt $\times$ parity
BW, kg								
Birth	37.6	36.2	39.7	39.9	1.65	0.69	0.05	0.59
d 2	38.7	36.2	40.8	40.8	0.93	0.36	0.02	0.36
d 10	44.9	44.0	46.3	48.2	1.02	0.67	0.03	0.28
d 20	57.1	57.3	58.9	60.5	1.15	0.52	0.09	0.62
ADG, kg/d								
Birth to d 2	0.55	0.02	0.50	0.29	0.367	0.34	0.78	0.68
d 2 to 10	0.71	0.82	0.61	0.95	0.092	0.03	0.89	0.24
d 10 to 20	0.96	0.97	1.02	1.05	0.082	0.30	0.78	0.82
Birth to d 20	1.01	1.07	1.02	1.02	0.068	0.68	0.79	0.65

¹Trt = dam dietary treatment, Parity = dam parity.

Table 4. The effect of feeding a prepartum diet containing a high (HI) or moderate (MOD) starch content to dairy cows on IGF-1, glucose, and insulin concentrations before a glucose tolerance test (GTT), and glucose and insulin responses to a GTT at d 2, 10 (± 2 d), and 20 (± 2 d) of life

Item	d 2			d 10			d 20			P-value ¹	
	HI	MOD		HI	MOD		HI	MOD	SE	Trt	Day
Before GTT											
Serum IGF-1, ng/mL	97.7 ^a	97.3 ^a		167 ^b	195 ^b		224 ^b	256 ^b	10	0.09	<0.01
Plasma glucose, mg/dL	95.2 ^a	96.1 ^a		106 ^b	116 ^b		120 ^b	114 ^b	4	0.78	<0.01
Plasma insulin, ng/mL	2.3	2.2		2.12	2.11		3.04	1.92	0.26	0.11	0.23
Response to GTT ²											
Glucose Cmax, mg/dL	142 ^a	151 ^a		152 ^b	165 ^b		180 ^c	186 ^c	5.7	0.16	<0.01
Glucose Tmax, min	3.7	3.1		3.8	3.1		3.4	3.1	0.3	0.02	0.60
Glucose delta, mg/dL	47.1 ^a	55.2 ^a		45.6 ^a	48.3 ^a		59.7 ^b	71.5 ^b	4.5	0.09	<0.01
Glucose delta/Tmax, mg/dL per min	14.5 ^a	17.9 ^a		13.6 ^a	15.8 ^a		18.1 ^b	23.5 ^b	1.5	0.02	<0.01
Glucose AUC, mg/dL $\times$ min	97.3 ^a	114 ^a		185 ^{ab}	207 ^{ab}		198 ^b	420 ^b	53	0.05	<0.01
Glucose clearance, %/min	0.63	0.78		0.7	0.94		0.96	0.91	0.13	0.20	0.36
Insulin Cmax, ng/mL	11.1 ^x	6.55 ^y		5.41 ^y	5.07 ^y		7.53 ^y	4.93 ^y	0.93	0.01	<0.01
Insulin Tmax, min	9.5	10.4		10.0	10.6		9.7	12.0	1.1	0.22	0.47
Insulin delta, mg/dL	8.8 ^x	4.35 ^y		3.29 ^y	2.96 ^y		4.48 ^y	3.01 ^y	0.83	0.01	<0.01
Insulin delta/Tmax, ng/mL per min	1.00 ^a	0.45 ^a		0.37 ^b	0.33 ^b		0.54 ^b	0.32 ^b	0.11	0.01	0.02
Insulin AUC, ng/mL $\times$ min	17.2	10.8		11.9	9.67		13.1	8.33	1.84	<0.01	0.22
Insulin clearance, %/min	1.93 ^a	1.62 ^a		2.74 ^b	2.74 ^b		2.84 ^b	2.12 ^b	0.42	0.39	<0.01
Insulin sensitivity, mg/min $\times$ ng/mL	3.24	7.07		8.51	14.3		12.7	10.6	2.1	0.24	0.08

^{a-c}Least squares means for day differ ($P < 0.05$) if superscripts within a row are different.
^{x,y}Least squares means for each Trt $\times$ day combination differ ($P < 0.05$) if superscripts within a row are different.
¹Trt = dam dietary treatment. The effects of parity and the interaction of Trt $\times$ parity were not significant for any measured variable and, therefore, are not presented.
²Cmax = maximum plasma concentration; Tmax = time of maximum concentration; delta = the maximum change from baseline; AUC = positive area under the concentration–time curve for 90 min.

Figure 2. Plasma glucose and insulin concentrations following an intravenous glucose tolerance test in female calves born to dams fed a high-starch (solid circle) or moderate-starch (open circle) diet prepartum on d 2 (column A), 10 (± 2 d; column B), and 20 (± 2 d; column C). Data are LSM $\pm$ SEM. Trt = dam dietary treatment. *Significant differences are indicated at $P < 0.05$.

between treatments on d 10 or 20. Insulin AUC was greater for HI compared with MOD regardless of calf age. Insulin clearance rate was not affected by treatment but increased between d 2 and 10. A tendency of the treatment $\times$ day interaction was observed for calculated insulin sensitivity ($P = 0.06$), but treatment effect was not significant at any day according to pairwise comparisons.

DISCUSSION

Within dairy production systems, it is common to offer a high-energy prepartum diet. Using pooled data from 7 studies, Cardoso et al. (2013) reported that cows fed high-energy prepartum diets, achieved through high fat or starch feeding, had elevated plasma concentrations of glucose and insulin prepartum. However, little is known about the effects of prepartum diets on offspring. Therefore, the objective of this study was to evaluate the effects of differing starch content of late gestation prepartum diets on offspring performance.

Neither diet fed to cows in the current study was restrictive; rather, both exceeded nutrient requirements. No difference in change in BCS was observed between enrollment and parturition. Cows were fed the prepartum diet for only 24 ± 3.2 d (SD) and 25 ± 4.1 d for HI and MOD, respectively, which may not have allowed for a detectable accretion or mobilization of body reserves. A treatment $\times$ parity interaction existed for plasma glucose concentration whereby multiparous dams fed HI had a greater glucose concentration compared with

MOD, but it was not different for primiparous dams. The cows used in the current study were a subset from a study with more animals where glucose concentrations were greater for HI as compared with MOD treatments regardless of parity (J. Haisan, W. Shi, and M. Oba, unpublished data). This suggests that this subset lacked statistical power to detect difference in glucose concentrations between treatments. Cows fed HI had greater plasma concentrations of insulin 12 d before parturition as compared with cows fed MOD. It is well established that dairy cows become insulin resistant as a means to supply the developing fetus and mammary gland with glucose (De Koster and Opsomer, 2013). Greater prepartum energy intake has been associated with greater insulin resistance even when BCS of cows is not changed (Salin et al., 2018), and greater energy intake prepartum can increase insulin concentrations (Holtenius et al., 2003; Cardoso et al., 2013) as seen in the current study.

Calf birth BW did not differ in the current study, which is in alignment with other studies evaluating prepartum dietary energy intake (Osorio et al., 2013). Fetal growth is dependent on transfer of nutrients from the dam via the placenta, with glucose being the primary energy substrate and its metabolism heavily regulated (Hay, 2006). Although most fetal growth occurs in the last 2 mo of gestation (Robinson et al., 1995), the diets fed in the current study were not deficient in energy or protein. Within the literature, studies evaluating diets deficient in protein and energy find reduced offspring BW with restriction (Spitzer et al., 1995; Freetly et

al., 2000; LeMaster et al., 2017). In contrast, when adequate energy is supplied, regardless of restricted protein supply, calf BW is not affected (Martin et al., 2007; Janovick and Drackley, 2010; Salin et al., 2018).

Basal concentrations of insulin, glucose, or IGF-1 were not different on d 2. This sampling occurred a minimum of 6 h following colostrum feeding, before milk was fed. It is well established that the amount and timing of colostrum feeding has marked effects on plasma metabolite concentrations of neonatal calves (Blum and Hammon, 2000). All calves were sampled in a fasted state, and managed alike, no difference was expected. Basal concentrations of IGF-1 and glucose increased between d 2 and 10. These findings are to be expected as milk intake also increased with age (Figure 1). Nutrient intake is the primary stimulant for IGF-1 (Smith et al., 2002), and milk replacer digestion would result in an increase in glucose concentrations as seen between d 2 and 10 of age.

Basal concentrations of glucose in calves at d 2 and 10 were correlated with maternal concentration of glucose at 12 d before parturition ($r = 0.38$, $P = 0.04$; $r = 0.30$, $P = 0.10$ for d 2 and 10, respectively). It is well established in human medicine that fetal exposure to gestational diabetes results in abnormal glucose homeostasis in offspring (Monteiro et al., 2016). As previously mentioned, cows in late gestation redirect glucose to the developing fetus and may experience a pseudo-gestational diabetic state characterized by increased circulating glucose concentrations. In other species, it has been found that this state may relate to changes in metabolites reaching the placenta and fetus, altering fetal and offspring metabolism (Newbern and Free-mark, 2011). Maternal glucose is the primary source of glucose for the fetus; it is transferred via facilitated diffusion with a close relationship between fetal glucose uptake and maternal concentrations (Bell and Bauman, 1997; Hay, 2006). In rats, it has been found that inducing slight hyperglycemia in late gestation results in increased fetal pancreatic and plasma insulin concentrations when studied in vitro (Bihoreau et al., 1986). When studied in vivo, rat offspring exposed to slight maternal hyperglycemia during late gestation show impaired insulin secretion following a GTT early in life and exhibit hyperglycemia long term (Gauguier et al., 1991). Therefore, it is possible that the correlation seen in the current study may indicate that fetal exposure to glucose in utero may result in hyperglycemia of calves in early life.

Glucose or insulin clearance rate nor the calculated insulin sensitivity index differed between HI and MOD. However, greater insulin C_{max}, AUC, and delta for HI, with no difference in glucose C_{max} or delta between treatments, suggest that HI calves required more in-

sulin to clear the same amount of infused glucose. In ruminant models, nutrient restriction of ewes during late gestation increased concentrations of glucose and insulin following a GTT in lambs (Gardner et al., 2005). Long et al. (2010b) reported that when beef cows were restricted in early to mid gestation, calves sampled at 15 mo of age had increased glucose clearance following a GTT. When sheep were overfed before conception through to parturition, mature lambs from overfed dams had reduced insulin sensitivity at 19 mo of age compared with lambs born to dams fed a maintenance diet (Long et al., 2010a). Although the long-term effects of the findings of the current study are unknown, these data support the hypothesis that maternal diet can influence offspring insulin sensitivity indicators across species, exhibiting short- and long-term effects.

In the current study, maternal insulin concentrations differed 12 d before parturition. In utero, insulin does not pass through the placenta to the fetus (Bell and Bauman, 1997; Hay, 2006). In in vitro studies using human placenta, infusion of insulin into the maternal compartment did not affect 3-O-methylglucose transfer rate; thus, it was concluded that placental glucose metabolism and transfer are not sensitive to insulin (Urbach et al., 1989). Fetal insulin is produced as a response to glucose transport to the fetus. Although few models have assessed oversupply of nutrients during only late gestation and the effect it has on pancreatic β cell function in neonates, the size and number of pancreatic β cells are determined by mid gestation (Ford et al., 2009). Therefore, although it is unlikely that fetal short-term exposure to increased maternal glucose in late gestation has lasting effects on the fetal pancreas, it is possible that sensitivity of the pancreas is altered short term based on the environment the fetus is exposed to and may contribute to some of the changes in insulin sensitivity indicators observed immediately following birth in the current study.

Although we cannot solely attribute the differences in calf response to a GTT to maternal plasma glucose concentrations because we did not detect differences in maternal concentrations in all animals, it should be noted that the maternal data have some limitations. The blood sample collected from dams before calving was collected only once during the study and, therefore, may not completely characterize the glucose status of dams. In the larger data set, with same sampling frequency, glucose differed between HI and MOD, so we cannot completely exclude the possibility that maternal glucose concentrations affect insulin sensitivity indicators of newborn calves. In addition, although we have attributed results to the starch content of the diet, the effects of starch and fiber are confounded within themselves, and thus, the difference in the extent of fiber

fermentation may have affected dam metabolism and blood metabolites.

Although the mechanism for newborn calves from dams fed high-starch diets exhibiting indicators of reduced insulin sensitivity is unknown, and whether long-term effects exist is unclear, previous studies of maternal hyperglycemia, obesity, and high-energy diet feeding during pregnancy in other species have shown abnormalities in offspring including increased fat mass, increased lipid deposition in the liver, and reduced insulin sensitivity (Elahi et al., 2009; McCurdy et al., 2009; Heerwagen et al., 2010). Although it cannot be ignored that mature ruminants rely on glucose less than the monogastric species commonly studied, in the context of a dairy cow, this is of interest because after calving cows often experience reduced insulin sensitivity as a means to mobilize lipids (De Koster and Opsomer, 2013). However, reduced insulin sensitivity may result in increased lipid mobilization and an increase in plasma nonesterified fatty acid concentrations, thus increasing their risk of ketosis and metabolic disorders. Therefore, these findings warrant further investigation in the dairy cow, particularly whether lasting effects exist on female offspring during lactation.

CONCLUSIONS

Feeding a high-starch prepartum diet to dams reduced indicators of insulin sensitivity of newborn calves as measured through a glucose tolerance test early in life. Although the exact mechanism is unknown, further research should be conducted to determine the potential long-term effects and implications of reduced insulin sensitivity in dairy calves and cows.

ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support by Alberta Milk (Edmonton, AB, Canada) and Alberta Livestock and Meat Agency (Edmonton, AB, Canada).

REFERENCES

- Ashino, N. G., K. N. Saito, F. D. Souza, F. S. Nakutz, E. A. Roman, L. A. Velloso, A. S. Torsoni, and M. A. Torsoni. 2012. Maternal high-fat feeding through pregnancy and lactation predisposes mouse offspring to molecular insulin resistance and fatty liver. *J. Nutr. Biochem.* 23:341–348.
- Bell, A. W., and D. E. Bauman. 1997. Adaptations of glucose metabolism during pregnancy and lactation. *J. Mammary Gland Biol. Neoplasia* 2:265–278.
- Bielmann, V., J. Gillian, N. R. Perkins, A. L. Skidmore, S. Godden, and K. E. Leslie. 2010. An evaluation of Brix refractometry instruments for measurement of colostrum quality in dairy cattle. *J. Dairy Sci.* 93:3713–3721.
- Bihoreau, M. T., A. Ktorza, A. Kervran, and L. Picon. 1986. Effects of gestational hyperglycemia on insulin secretion in vivo and in vitro by fetal rat pancreas. *Am. J. Physiol.* 251:E86–E91.
- Blum, J. W., and H. Hammon. 2000. Colostrum effects on the gastrointestinal tract, and on nutritional, endocrine and metabolic parameters in neonatal calves. *Livest. Prod. Sci.* 66:151–159.
- Bossaert, P., J. L. M. R. Leroy, S. De Capeneere, S. De Vlieghe, and G. Opsomer. 2009. Differences in the glucose-induced insulin response and the peripheral insulin responsiveness between neonatal calves of the Belgian Blue, Holstein-Friesian, and East Friesian breeds. *J. Dairy Sci.* 92:4404–4411.
- Cardoso, F. C., S. J. LeBlanc, M. R. Murphy, and J. K. Drackley. 2013. Prepartum nutritional strategy affects reproductive performance in dairy cows. *J. Dairy Sci.* 96:5859–5871.
- Chavatte-Palmer, P., M. A. Velazquez, H. Jammes, and V. Duranton. 2018. Review: Epigenetics, developmental programming and nutrition in herbivores. *Animal* 12(Suppl. 2):s363–s371. <https://doi.org/10.1017/S1751731118001337>.
- Christoffersen, B., U. Ribel, K. Raun, V. Golozubova, and G. Pacini. 2009. Evaluation of different methods for assessment of insulin sensitivity in Gottingen minipigs: Introduction of a new, simpler method. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 297:R1195–1201.
- De Koster, J. D., and G. Opsomer. 2013. Insulin resistance in dairy cows. *Vet. Clin. North Am. Food Anim. Pract.* 29:299–322.
- Elahi, M. M., F. R. Cagampang, D. Mukhar, F. W. Anthony, S. K. Ohri, and M. A. Hanson. 2009. Long-term maternal high-fat feeding from weaning through pregnancy and lactation predisposes offspring to hypertension, raised plasma lipids and fatty liver in mice. *Br. J. Nutr.* 102:514–519.
- Ford, S. P., L. Zhang, M. Zhu, M. M. Miller, D. T. Smith, B. W. Hess, G. E. Moss, P. W. Nathanielsz, and M. J. Mijland. 2009. Maternal obesity accelerates fetal pancreatic β -cell but not α -cell development in sheep: Prenatal consequences. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 297:R835–R843.
- Freetly, H. C., C. L. Ferrell, and T. G. Jenkins. 2000. Timing of realimentation of mature cows that were feed-restricted during pregnancy influences birth weights and growth rates. *J. Anim. Sci.* 78:2790–2796.
- Funston, R. N., D. M. Larson, and K. A. Vonnahme. 2010. Effects of maternal nutrition on conceptus growth and offspring performance: Implications for beef cattle production. *J. Anim. Sci.* 88:E205–E215.
- Gardner, D. S., K. Tingey, B. W. Van Bon, S. E. Ozanne, V. Wilson, J. Dandrea, D. H. Keisler, T. Stephenson, and M. E. Symonds. 2005. Programming of glucose-insulin metabolism in adult sheep after maternal undernutrition. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 289:947–954.
- Gauguier, D., M. T. Bihoreau, L. Picon, and A. Ktorza. 1991. Insulin secretion in adult rats after intrauterine exposure to mild hyperglycemia during late gestation. *Diabetes* 40:109–114.
- Hay, W. W. 2006. Placental-fetal glucose exchange and fetal glucose metabolism. *Trans. Am. Clin. Climatol. Assoc.* 117:321–339.
- Heerwagen, M. J., M. R. Miller, L. A. Barbour, and J. E. Friedman. 2010. Maternal obesity and fetal metabolic programming: A fertile epigenetic soil. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 299:R711–722.
- Holtenius, K., S. Agenes, C. Delavaud, and Y. Chilliard. 2003. Effects of feeding intensity during the dry period. 2. Metabolic and hormonal responses. *J. Dairy Sci.* 86:883–891.
- Hough, R. L., F. D. McCarthy, H. D. Kent, D. E. Eversole, and M. L. Wahlberg. 1990. Influence of nutritional restriction during late gestation on production measures and passive immunity in beef cattle. *J. Anim. Sci.* 68:2622–2627.
- Inabu, Y., A. Saegusa, K. Inouchi, S. Koike, M. Oba, and T. Sugino. 2017. Plasma concentrations of glucagon-like peptide 1 and 2 in calves fed calf starters containing lactose. *J. Dairy Sci.* 100:9361–9371.
- Janovick, N. A., Y. R. Boisclair, and J. K. Drackley. 2011. Prepartum dietary energy intake affects metabolism and health during the pe-

- riparturient period in primiparous and multiparous Holstein cows. *J. Dairy Sci.* 94:1385–1400.
- Janovick, N. A., and J. K. Drackley. 2010. Prepartum dietary management of energy intake affects postpartum intake and lactation performance by primiparous and multiparous Holstein cows. *J. Dairy Sci.* 93:3086–3102.
- LeMaster, C. T., R. K. Taylor, R. E. Ricks, and N. M. Long. 2017. The effects of late gestation maternal nutrient restriction with or without protein supplementation on endocrine regulation of newborn and postnatal beef calves. *Theriogenology* 87:64–71.
- Long, N. M., L. A. George, A. B. Uthlaut, D. T. Smith, M. J. Nijland, P. W. Nathaniels, and S. P. Ford. 2010a. Maternal obesity and increased nutrient intake before and during gestation in the ewe results in altered growth, adiposity, and glucose tolerance in adult offspring. *J. Anim. Sci.* 88:3546–3553.
- Long, N. M., M. J. Prado-Cooper, C. R. Krehbiel, and R. P. Wettemann. 2010b. Effects of nutrient restriction of bovine dams during early gestation on postnatal growth and regulation of plasma glucose. *J. Anim. Sci.* 88:3262–3268.
- Mann, S., F. A. Leal Yepes, T. R. Overton, J. J. Wakshlag, A. L. Lock, C. M. Ryan, and D. V. Nydam. 2015. Dry period plane of energy: Effects on feed intake, energy balance, milk production, and composition in transition dairy cows. *J. Dairy Sci.* 98:3366–3382.
- Martin, J. L., K. A. Vonnahme, D. C. Adams, G. P. Lardy, and R. N. Funston. 2007. Effect of dam nutrition on growth and reproductive performance of heifer calves. *J. Anim. Sci.* 85:841–847.
- McCurdy, C. E., J. M. Bishop, S. M. Williams, B. E. Grayson, M. S. Smith, J. E. Friedman, and K. L. Grove. 2009. Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. *J. Clin. Invest.* 119:323–335.
- McNamara, S., F. P. O'Mara, M. Rath, and J. J. Murphy. 2003. Effects of different transition diets on dry matter intake, milk production and milk composition in dairy cows. *J. Dairy Sci.* 86:2397–2408.
- Monteiro, L. J., J. E. Norman, G. E. Rice, and S. E. Illanes. 2016. Fetal programming and gestational diabetes mellitus. *Placenta* 48:S54–S60.
- NRC (National Research Council). 2001. *Nutrient Requirements of Dairy Cattle*. 7th ed. Natl. Acad. Press, Washington, DC.
- Newbern, D., and M. Freemark. 2011. Placenta hormones and the control of maternal metabolism and fetal growth. *Curr. Opin. Endocrinol. Diabetes Obes.* 18:409–416.
- Nivoit, P., C. Morens, F. A. Van Assche, E. Jansen, L. Poston, C. Remacle, and B. Reusens. 2009. Established diet-induced obesity in female rats leads to offspring hyperphagia, adiposity and insulin resistance. *Diabetologia* 52:1133–1142.
- Osorio, J. S., E. Trevisi, M. A. Ballou, G. Bertoni, J. K. Drackley, and J. J. Looor. 2013. Effect of the level of maternal energy intake prepartum on immunometabolic markers, polymorphonuclear leukocyte function, and neutrophil gene network expression in neonatal Holstein heifer calves. *J. Dairy Sci.* 96:3573–3587.
- Pires, J. A. A., A. H. Souza, and R. R. Grummer. 2007. Induction of hyperlipidemia by intravenous infusion of tallow emulsion causes insulin resistance in Holstein cows. *J. Dairy Sci.* 90:2735–2744.
- Robinson, J., S. Chidzanja, K. Kind, F. Lok, P. Owens, and J. Owen. 1995. Placental control of fetal growth. *Reprod. Fertil. Dev.* 7:333–344.
- Salin, S., A. Vanhatalo, S. Jaakkola, K. Elo, J. Taponen, R. C. Boston, and T. Kokkonen. 2018. Effects of dry period energy intake on insulin resistance, metabolic adaptation, and production responses in transition dairy cows on grass silage-based diets. *J. Dairy Sci.* 101:11364–11383.
- Smith, J. M., M. E. Van Amburgh, M. C. Diaz, M. C. Lucy, and D. E. Bauman. 2002. Effect of nutrient intake on the development of the somatotrophic axis and its responsiveness to GH in Holstein bull calves. *J. Anim. Sci.* 80:1528–1537.
- Spitzer, J. C., D. G. Morrison, R. P. Wettemann, and L. C. Faulkner. 1995. Reproductive responses and calf birth and weaning weights as affected by body condition at parturition and postpartum weight gain in primiparous beef cows. *J. Anim. Sci.* 73:1251–1257.
- Takahashi, H., Y. Kurose, S. Kobayashi, T. Sugino, M. Kojima, K. Kangawa, Y. Hasegawa, and Y. Terashima. 2006. Ghrelin enhances glucose-induced insulin secretion in scheduled meal-fed sheep. *J. Endocrinol.* 189:67–75.
- Urbach, J., L. Mor, N. Ronen, and J. M. Brandes. 1989. Does insulin affect placental glucose metabolism and transfer? *Am. J. Obstet. Gynecol.* 161:953–959.
- Vickers, L. A., D. M. Weary, D. M. Veira, and M. A. von Keyserlink. 2013. Feeding a higher forage diet prepartum decreases incidences of subclinical ketosis in transition dairy cows. *J. Anim. Sci.* 91:886–894.
- Yunta, C., M. Terré, and A. Bach. 2015. Short- and medium-term changes in performance and metabolism of dairy calves offered different amounts of milk replacers. *Livest. Sci.* 181:249–255.