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Effects of maternal nutrition on development of gastrointestinal tract of bovine fetus at different stages of gestation

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ABSTRACT

This study was developed aiming to evaluate the effects of maternal feed-restriction on development of gastrointestinal tract (GIT) of bovine fetus at different gestational stages. Feed-restricted cows were fed 1.2 times the maintenance level while the control group was fed ad libitum. Pregnant cows were slaughtered at 136, 189, 239, and 269 days of gestation and gastrointestinal tracts of the fetuses were evaluated. No effects of maternal nutrition on body weight ($P=0.17$) and body length ($P=0.13$) of the fetuses were observed. No major effects of feed restriction on GIT mass of the fetuses were observed ($P=0.51$). However, the weight of small intestine per unit of body weight was 11.24% greater ($P=0.04$) in fetuses from restricted dams. Additionally, the length of small intestine and its villi were 12.93% and 16.44% respectively greater ($P<.001$) in fetuses from restricted dams compared to those from non-restricted dams. These data indicates that maternal feed-restriction does not affect the development of most of fetal gastrointestinal parts besides small intestine which in turn increases its surface area as a response of maternal feed restriction.

1. Introduction

During the early phase of fetal stage critical events for normal conceptus development occur including differentiation, vascularization, fetal organogenesis, and placental development (Funston et al., 2010). Several studies have shown that fetuses from dams subjected to nutrient restriction during early to midgestation have decreased growth of the gastrointestinal tract (Avila et al., 1989; Harding et al., 1985; Trahair et al., 1997; Wang et al., 2008), and even with postnatal nutritional intervention, the suboptimal growth causes permanent changes in gastrointestinal functions such as epithelial permeability (Trahair et al., 1997).

Fetal growth restriction due to maternal nutrition has been reported as a problem in livestock production (Du et al., 2010; Wu et al., 2006) since a variety of production conditions may lead to a scenario of fetal growth restriction. As an example, in tropical regions where beef cattle are raised mainly in grazing systems, pregnant cows usually experience feed restriction during the mid-gestation period which overlaps with a season of low quantity and quality of forage (Duarte et al., 2012). Therefore, since in cattle the absorption of intact macromolecules such as immunoglobulin across the intestinal

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epithelium is possible for approximately 24 h after the calf is born, the well development of gastrointestinal tract during intrauterine stages is crucial to reduce neonatal morbidity and mortality.

Moreover, since the gastrointestinal tract serves as the main site for nutrient absorption, the changes on the development of gastrointestinal tract at the fetal stage may permanently affect the offspring performance and efficiency of nutrient utilization (Wang et al., 2008; Wu et al., 2006) impairing efficiency of animal production. However, there is a very little information regarding this topic using beef cattle as a model (Meyer et al., 2010). The objective of this study was to evaluate maternal nutrition effects on the development of gastrointestinal tract of bovine fetus at different stages of gestation.

2. Material and methods

2.1. Animals and management

All animal care and handling procedures were approved by the Animal Care and Use Committee of the Department of Animal Science of the Universidade Federal de Viçosa, Brazil.

Thirty-two multiparous Nellore cows with average initial body weight of 451 ± 67 (mean ± SE) kg, age of 5.6 ± 1.9 years and body condition score of 4.6 ± 1.1 (from 1 to 9 scale) were used. Pregnancy was detected by ultrasound 25 days after mating and the day of mating was considered as day 0 of pregnancy. On day 27 of gestation cattle were confined in collective pens (48 m^2, 6 cows per pen) with individual electronic head gate system (Kloppen Soluções Tecnológicas, Pirassununga, SP, Brazil) for adaptation to individual feeders. At day 47 of gestation, cows were randomly assigned into two groups with different feeding levels where half of the cows ($n=16$) were fed at 1.2 times maintenance (NRC, 2000) and the other half were fed ad libitum ($n=16$). The restricted feeding level used was estimated to be enough to maintain the pregnancy of the dam throughout the experiment avoiding abortion at any period of gestation. Feed intake of feed-restricted dams was 10.8 ± 1.5 g of dry matter/kg of shrunk body weight (animal's equivalent weight after overnight fast without feed; NRC, 2000) while for dams fed at libitum the feed intake was 16.0 ± 2.0 g of dry matter/kg of shrunk body weight. Cows were fed the same diet with differences only in the feeding level.

Every 28 days cows were weighed in the morning before feeding and after a 16 h solid fast to obtain the shrunk body weight and the feed intake was adjusted based on values of shrunk body weight to maintain the feed-restriction throughout the entire gestational period.

Experimental diets consisted of 64.8% of total digestible nutrients and 13.5% of crude protein on dry matter (DM) basis and composed of corn silage (84.3% DM basis), ground corn (8.5% DM basis), soybean meal (5.1% DM basis), urea/ammonium sulfate (1.4% DM basis) and mineral mixture (0.7% DM basis). The mineral mixture was composed of 15% calcium, 9% phosphorus, 0.53% zinc, 0.13% manganese, 0.2% copper, and 100 mg/kg of cobalt.

To evaluate the effects of maternal feed-restriction on development of gastrointestinal tract at different stages of gestation, pregnant cows were slaughtered at four gestational periods. Each feeding level group (maintenance and ad libitum) was randomly divided into four groups with four cows in each group to be slaughter at 136, 189, 239, and 269 days of gestation. Cows were slaughtered at Universidade Federal de Viçosa abattoir using a captive bolt stunning and exsanguination. Pre-harvest handling was in accordance with good animal welfare practices, and slaughtering procedures followed the Sanitary and Industrial Inspection Regulation for Animal Origin Products (Brasil, 1997).

2.2. Tissue sample and data collection

After the exsanguination the gravid uterus was immediately collected and fetus was removed. The dissection of the fetus and isolation of the gastrointestinal tract was performed similarly to that described by Meyer et al. (2010). Briefly, Fetuses were dissected and the whole gastrointestinal tract was collected and gently stripped of fat and digesta. The stomach complex was isolated from the esophagus and the intestine at the pyloric valve and divided into reticulum-rumen, omasum, abomasum and each component was gently emptied and weighed. Small and large intestines were isolated and weigh and length was recorded separately. Then, small intestine was divided into duodenum, jejunum and ileum similarly to that described by Soto-Navarro et al. (2004) as it follows. The duodenum was identified as the segment from the pylorus to a point directly adjacent to the entry of the gastrosplenic vein into the mesenteric vein. The jejunum was the segment from the caudal end of the duodenum to the junction of jejunum and ileum. This junction was determined by measuring 15 cm up the mesenteric vein from the convergence of the mesenteric and ileocecal veins and then up the mesenteric arcade to the point of intestinal intersection. From this point, a 150-cm measurement was made caudally down the small intestine, which was identified as the terminal end of the jejunum and the beginning of the ileum. The ileum measurement was terminated at the ileocecal junction.

2.3. Small intestine villi morphology

Tissue samples from jejunum, duodenum and ileum were fixed in fresh 10% (w/v) formalin in phosphate buffer (pH 7.4) and embedded using the HistoResin Mounting Kit (Leica®, Heidelberg, BW, Germany). Fragments of small intestine were carefully embedded to allow the presence of great number of villi longitudinally oriented in each section. Sections were cut at 3 μm, stained with toluidine blue, and observed under light microscopy. For each segment of small intestine (duodenum, jejunum and ileum) of each animal only intact villus with evident lamina propria, base and top were selected to measure the villi length. Photomicrographs were taken with a CMOS digital camera (Biocam GmbH®, BAV, Germany) coupled to an Olympus BX50 light microscope (Center Valley, PA, United States). Ten fields and ten villi per field were randomly selected to measure the villus length.

Images were analyzed by using the ImageJ® software (National Institutes of Health, USA) and a total of 300 villi per animal (3 segments × 10 fields × 10 villi per field) were measured. Measurements of curved villus were performed by using the segmented line selection and analyzed by the straighten tool of ImageJ®.

2.4. Statistical analysis

Data was analyzed through a model including the fixed effects of gestational period, maternal nutrition, and their interaction as described below:

$$Y_{ijk} = \mu + D_i + G_j + (D \times G)_{ij} + e_{ijk}$$

where D_i is the ith level of the fixed effect of diet, G_j the jth level of the fixed effect of gestation period and e_{ijk} the random error associated with Y_{ijk}

This model was used to all studied response variables besides villi length. In addition to all the effects in the model, the fixed effect covariate of body length of the fetus was included in order to adjust the values of villi length. For each response variable, outliers were removed in order to achieve normality using Shapiro–Wilks test at $\alpha = 0.05$. Least square means were estimated for all effects and compared using Tukey's method at $\alpha = 0.05$. All statistical procedures were performed using the MIXED procedure from SAS 9.2 (Statistical Analysis System Institute, Inc., Cary, NC, USA).

3. Results

At the beginning of the experiment (47 days of gestation) cows had similar average shrunk body weight ($P = 0.52$) which was 437 ± 15 kg for the non-restricted cows and 438 ± 14 kg for feed-restricted cows. However, as a result of the feeding levels applied, shrunk body weight was different ($P = 0.003$) among feeding level groups with average of 563 ± 16 kg for non-restricted cows and 482 ± 16 kg for feed-restricted cows. This was due to the difference of shrunk body weight daily gain ($P < .0001$) among feeding level groups which was 0.86 ± 0.04 kg/day for non-restricted cows and 0.26 ± 0.04 kg/day for feed-restricted cows. Additionally, comparisons within each period of gestation evaluated showed that cows fed ad libitum had greater ($P < .0001$) shrunk body weight daily gain than feed-restricted cows at all gestational periods evaluated (Table 1), which demonstrates that cows fed 1.2 times maintenance were feed-restricted during the entire gestational period. Together, these data clearly shows the effectiveness of feeding restriction applied in this study.

Table 1
Shrunk body weight daily gain of pregnant Nellore cows fed at different days of gestation and feeding level.

Feeding level	Days of gestation			
	136	189	239	269
Shrunk body weight gain, kg/day				
Ad libitum	0.93 ± 0.09	0.79 ± 0.09	0.85 ± 0.09	0.87 ± 0.09
Maintenance	0.29 ± 0.09	0.18 ± 0.09	0.32 ± 0.09	0.29 ± 0.09
P-value	< 0.001	< 0.001	< 0.001	< 0.001

Significant interaction among feeding level and days of gestation was observed ($P = 0.02$) for body weight of the fetuses. The interaction analysis showed that only at 269 days of gestation fetuses from dams fed ad libitum were heavier (30.47 ± 1.03 kg) than those from feed-restricted dams (23.67 ± 1.03 kg) and no differences were observed in the body weight of fetuses from restricted and non-restricted dams at 136, 189, and 239 days of gestation. Significant interaction ($P = 0.02$) among feeding level and days of gestation was also observed for body weight:body length ratio (Table 2). The difference in body weight of the fetuses observed only at 269 days of gestation is likely because the most fetal growth occurs during the last three months of gestation (Ferrell et al., 1976).

The body length of the fetuses were not affected ($P = 0.13$) by maternal nutrition. However, as expected, the body length of the fetuses increased ($P < .0001$) as the gestation advanced (Table 2).

There was no effect of maternal nutrition ($P = 0.05$) on the absolute weight of gastrointestinal tract, stomach complex ($P = 0.79$), reticulum-rumen ($P = 0.92$), omasum ($P = 0.18$), abomasum ($P = 0.44$), small intestine ($P = 0.32$) and large intestine ($P = 0.65$) (Table 2). When expressed as a function of body weight, no effects of maternal nutrition were found on gastrointestinal tract ($P = 0.1126$), stomach complex ($P = 0.97$), reticulum-rumen ($P = 0.97$), omasum ($P = 0.52$), abomasum ($P = 0.82$) and large intestine ($P = 0.54$). However, the small intestine expressed as function of body weight was greater ($P = 0.04$) in fetuses from restricted dams compared to those from non-restricted dams (Table 2). Similarly, the lengths of small intestine ($P = 0.0017$) and its villi ($P < .0001$) were increased in fetuses from restricted dams (Table 2).

The absolute weight of gastrointestinal tract and abomasum increased ($P < .0001$) with days of gestation but was unaffected ($P = 0.58$) when analyzed as a function of body weight (Table 2). The absolute weight of stomach complex ($P < .0001$), reticulum-rumen ($P < .0001$), and omasum ($P < .0001$) increased with days of gestation. However, the weight per unit of body weight of stomach ($P = 0.0002$), reticulum-rumen ($P < .0001$), and omasum ($P < .0001$) decreased with days of gestation (Table 2). The absolute weight of abomasum ($P < .0001$) and small intestine ($P < .0001$) increased with days of gestation. However, no differences were observed among days of gestation for weight of abomasum ($P = 0.36$) and small intestine ($P = 0.07$) when analyzed as a function of body weight (Table 2).The lengths of small intestine ($P < .0001$) and its villi ($P < .0001$) increased with days of gestation (Table 2).

4. Discussion

The phase of a rapid growth of gastrointestinal tract occurs at the third trimester of gestation in species that has a long gestational period (Weaver et al., 1991). However, no effects of maternal feed restriction were observed on the weight of the gastrointestinal tract and its components at any of the gestational stages evaluated. According to Meyer et al. (2010) organogenesis mainly

Table 2
Effects of feeding level and days of gestation on final shrunk body weight of pregnant cows and fetal development.

Item	Feeding level		Days of gestation				P–value		
	Ad libitum	Feed-restricted	136	189	239	269	Feeding level	Days of gestation	Feeding level × days of gestation
Final shrunk body weight of the cows (kg)	575 ± 16.9^{a}	480 ± 16.9^{b}	555.6 ± 23.9	551 ± 23.9	508 ± 23.9	494 ± 23.9	0.001	0.20	0.41
Fetus body weight (kg)	13.0 ± 0.66^{a}	14.36 ± 0.66^{a}	1.50 ± 0.93	6.33 ± 0.93	19.9 ± 0.93	27.1 ± 0.93	0.17	< .0001	0.01
Fetus body length (cm)	63.6 ± 1.20^{a}	60.9 ± 1.20^{a}	32.4 ± 1.70^{d}	52.6 ± 1.70^{c}	77.4 ± 1.70^{b}	86.6 ± 1.70^{a}	0.13	< .0001	0.25
Fetus body weight/body length ratio	0.19 ± 0.01^{a}	0.18 ± 0.01^{a}	0.05 ± 0.01	0.12 ± 0.01	0.25 ± 0.01	0.31 ± 0.01	0.34	< .0001	0.02
			Fetal gastrointestinal tract measurements						
Gastrointestinal tract (g)	333 ± 13.8^{a}	346 ± 13.8^{a}	40.5 ± 20.2^{d}	159 ± 18.7^{c}	510 ± 18.7^{b}	650 ± 20.2^{a}	0.51	< .0001	0.54
g/kg of body weight	25.2 ± 0.75^{a}	27.0 ± 0.75^{a}	27.3 ± 1.06^{a}	25.3 ± 1.06^{a}	25.9 ± 1.06^{a}	25.8 ± 1.06^{a}	0.11	0.58	0.67
Total stomach (g)	119 ± 5.16^{a}	117 ± 5.16^{a}	19.5 ± 7.30^{d}	67.6 ± 7.30^{c}	164.2 ± 7.30^{b}	221 ± 7.30^{a}	0.79	< .0001	0.28
g/kg of body weight	11.4 ± 0.38^{a}	11.4 ± 0.38^{a}	13.6 ± 0.54^{a}	12.0 ± 0.54^{ab}	10.1 ± 0.54^{b}	10.1 ± 0.54^{b}	0.97	0.0002	0.61
Reticulum–rumen (g)	55.8 ± 2.48^{a}	55.4 ± 2.48^{a}	11.4 ± 3.51^{d}	34.6 ± 3.51^{c}	78.8 ± 3.51^{b}	97.6 ± 3.51^{a}	0.92	< .0001	0.45
g/kg of body weight	5.18 ± 0.19^{a}	5.19 ± 0.19^{a}	7.59 ± 0.26^{a}	5.51 ± 0.26^{b}	4.00 ± 0.26^{c}	3.65 ± 0.26^{c}	0.97	< .0001	0.20
Omasum (g)	19.3 ± 1.07^{a}	17.2 ± 1.11^{a}	3.72 ± 1.51^{c}	13.0 ± 1.51^{b}	26.7 ± 1.51^{a}	29.7 ± 1.63^{a}	0.18	< .0001	0.20
g/kg of body weight	1.73 ± 0.11^{a}	1.83 ± 0.11^{a}	2.49 ± 0.16^{a}	2.08 ± 0.16^{a}	1.36 ± 0.16^{b}	1.20 ± 0.16^{b}	0.52	< .0001	0.79
Abomasum (g)	42.2 ± 1.07^{a}	41.0 ± 10.7^{a}	4.43 ± 1.46^{d}	20.0 ± 1.46^{c}	54.7 ± 1.57^{b}	87.2 ± 1.57^{a}	0.44	< .0001	0.29
g/kg of body weight	3.09 ± 0.15^{a}	3.14 ± 0.15^{a}	2.89 ± 0.21^{a}	3.18 ± 0.21^{a}	2.99 ± 0.21^{a}	3.39 ± 0.21^{a}	0.82	0.36	0.47
Small intestine (g)	158 ± 7.11^{a}	168 ± 6.84^{a}	16.2 ± 9.67^{d}	69.2 ± 9.67^{c}	259 ± 9.67^{b}	307 ± 10.4^{a}	0.32	< .0001	0.87
g/kg of body weight	11.2 ± 0.46^{b}	12.6 ± 0.46^{a}	10.9 ± 0.65^{a}	11.1 ± 0.65^{a}	13.2 ± 0.65^{a}	12.4 ± 0.65^{a}	0.04	0.07	0.37
Large intestine (g)	59.4 ± 3.51^{a}	61.6 ± 3.38^{a}	5.07 ± 4.78^{d}	21.8 ± 4.78^{c}	87.0 ± 4.78^{b}	128 ± 5.16^{a}	0.65	< .0001	0.39
g/kg of body weight	4.01 ± 0.19^{a}	4.18 ± 0.19^{a}	3.45 ± 0.27^{b}	3.42 ± 0.27^{b}	4.38 ± 0.27^{ab}	5.14 ± 0.27^{a}	0.54	0.0003	0.98
Small intestine length (cm)	672 ± 20.0^{b}	771 ± 20.0^{a}	361 ± 28.3^{d}	612 ± 28.3^{c}	859 ± 28.3^{b}	1053 ± 28.3^{a}	0.002	< .0001	0.27
Small intestine villi length (μm)	356 ± 10.2^{b}	430 ± 10.2^{a}	323 ± 54.1	377 ± 22.3	415 ± 30.2	458 ± 45.0	< .0001	0.40	0.83

^{a,b,c,d} Means within a row and effect lacking a common superscript letter differ significantly ($P > 0.05$).

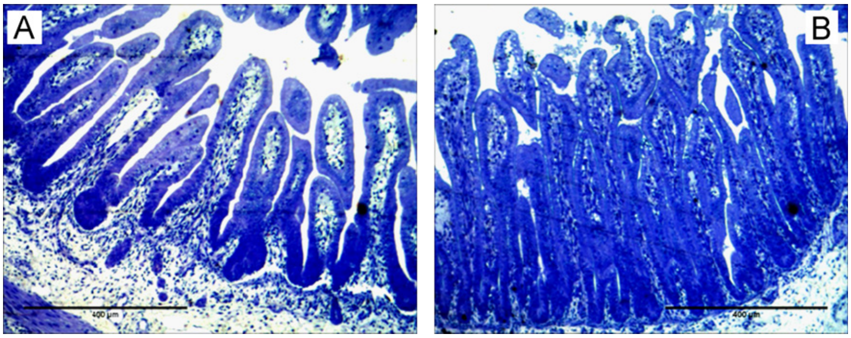

Fig. 1. Representative photomicrograph (10 ×) showing a contrast of small intestine villi of bovine fetus from non-restricted (A) and feed-restricted (B) dams at 190 days of gestation.

occurs at early to mid-gestation. Thus, in the current study when dams were feed-restricted (mid- to late-gestation) the fetal organogenesis may had already been accomplished and the gastrointestinal tract was less vulnerable to changes due to maternal nutrient restriction. Additionally, it has been suggested that even though the dam is undernourished the placental system can compensate to provide the fetus adequate amount of nutrients mainly by increasing the number of caruncles (Bassett, 1991; Clarke et al., 1998) which also possibly have contributed for the lack of effects of maternal feed restriction on fetal gastrointestinal tract mass.

Since the gastrointestinal tract is responsible for nutrient absorption it must have an adequate surface area and therefore, intestinal length is an important characteristic for animal performance (Trahair et al., 1997). Even though no differences was observed among dietary treatments for gastrointestinal tract mass, a greater length of small intestine in fetus of restricted dams was observed, which likely indicates a more efficient growth to compensate the low supply of nutrients. Because the mucosal epithelium is the most labile wall component in the small intestine, intrauterine insults such as feed restriction can alter growth of mucosal components on intestinal the surface area including the size and density of the villi (Trahair et al., 1997). It has been reported previously that intestine from fetuses of restricted dams has an increase in proliferation and vascularization (Meyer et al., 2010) which would explain not only the greater length of small intestine of fetuses from restricted dams but also their greater villi length (Fig. 1). Additionally, the lack of correlation ($P=0.46$) between villi length and body length of fetuses and the use of body length as covariate for villi length indicates that differences in villi length occurred only as a result maternal feed-restriction (Table 2).

Hammer et al. (2011) have shown that offspring from undernourished dams had increased immunoglobulin transfer compared to non-restricted fed dams. Therefore, from the results observed in the current experiment it can be inferred that fetal gastrointestinal system may be programmed in nutrient restricted animals to be more efficient in extracting nutrients, specifically large molecules like immunoglobulins immediately postnatal (Funston et al., 2010), although this has not been determined in this trial.

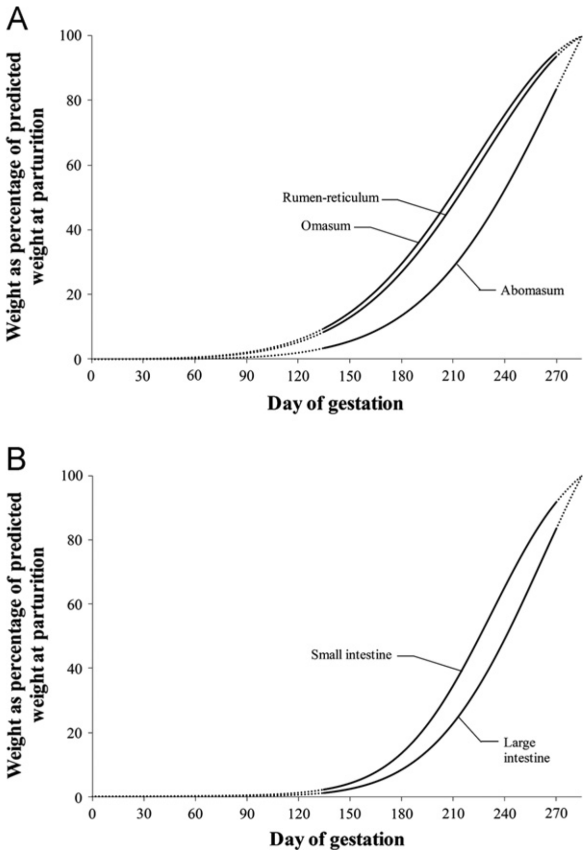

Fig. 2. Relationship among weights of the reticulum-rumen, omasum and abomasum (A) and small and large intestines (B), expressed as percentages of predicted weights at parturition and days of gestation. Solid lines represent actual data range and dash lines are extrapolated from the data.

Immature ruminants are functionally non-ruminants. To become functional, the stomach compartments, mainly the rumen, must be inoculated with microorganisms, including bacteria, fungi, and protozoa which usually occurs after birth when calves contacts solid feedstuff. Therefore, the lack of effects of maternal feed restriction on the weight of stomach complex and its components may be due to the non-functionality of these compartments at fetal stage since, theoretically, there is no need to expand the surface area of the stomach to increase nutrients absorption as occurs in the small intestine.

With regard to days of gestation, the data of the current study show a disproportionally growth between the stomach complex and the body of the fetus through the pregnancy period (Table 2). When analyzed separately, the weight the stomach parts per unit of body weight of the rumen-reticulum and omasum decreased as the day of gestation increased, suggesting that these compartments have a faster growth at early stages of gestation. Moreover, the decrease of proportional weights (g/kg of body weight) might be due to the non-functionality of the stomach complex at intrauterine stages of life as stated previously. Conversely, the abomasum and small intestine grew proportionally to the fetus as no differences were observed for the weight of the abomasum and small intestine per unit of body weight throughout the gestational period (Table 2). As expected, the length of small intestine and its villi also increased as the days of gestation increased (Table 2).

For a better visualization of the development of different compartments of fetal gastrointestinal tract throughout the gestational period, weights of gastrointestinal tract parts at parturition (285 days) were estimated by extrapolation of a logistic non-linear regression (Koong et al., 1975). The values obtained were 116.1 g, 38.6 g, 126.1 g, 354.5 g and 211.7 g for the reticulum-rumen, omasum, abomasum, small intestine and large intestine, respectively. Weights of these compartments at different days of gestation were then expressed as percentages of their predicted final weight and presented graphically indicating that reticulum-rumen and omasum development preceded abomasums development (Fig. 2). Similarly, the small intestine development also preceded the large intestine development. Together, these results support the importance of the abomasum in addition to the small intestine as the main source of nutrients absorption for ruminant animals possessing development priory when compared to the other gastrointestinal compartments.

5. Conclusion

The data suggests that maternal nutrient restriction affects the development of fetal small intestine without major effects on the development of gastrointestinal tract as a whole. Fetal small intestine increase surface area as a response of maternal feed restriction. So far, is not possible to define strategies of supplementation during the pregnancy visioning a better development of the fetal gastrointestinal tract which requires further studies to clarify cellular and molecular mechanisms responsible for changes on fetal gastrointestinal tract due to maternal nutrition.

Conflict of interest statement

The authors have declared that no conflict of interest exists.

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