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## **Colostrum yield and piglet growth during lactation are related to gilt metabolic and hepatic status prepartum**

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# Colostrum yield and piglet growth during lactation are related to gilt metabolic and hepatic status prepartum<sup>1</sup>

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**ABSTRACT:** It was hypothesized that colostrum production could be influenced by sow peripartum endocrine, metabolic, and hepatic status. The plant extract silymarin was shown to influence endocrine and hepatic status in several species. The aims of the present study were to investigate the effects of silymarin intake during late pregnancy on sow hormonal and hepatic status and to determine whether relations exist between sow hepatic and metabolic status during the peripartum period and colostrum yield and piglet performances during lactation. From d 107 of pregnancy until farrowing, nulliparous sows were either fed 12 g/d of silymarin (SIL;  $n = 15$ ) or no treatment (Control;  $n = 12$ ). Piglet BW was recorded directly after birth, 24 h after birth of the first piglet, and at 7, 14, and 21 d of lactation. Blood samples were collected from sows on d 107 and 109 of pregnancy, daily from d 111 of pregnancy until d 2 of lactation, and on d 7 and 21 of lactation. They were assayed for endocrine, metabolic, and hepatic variables. Colostrum yield was estimated during 24 h starting at the onset of farrowing. Silymarin did not influence colostrum yield ( $3.7 \pm 0.3$  kg) or gross composition ( $P > 0.10$ ), nor did it affect serum prolactin concentrations or

plasma concentrations of progesterone, estradiol-17 $\beta$ , or cortisol ( $P > 0.10$ ). Mean litter BW gain was lower ( $P < 0.05$ ) during the first week and tended ( $P < 0.10$ ) to be lower during the second week of lactation in litters from SIL sows. Silymarin had no effect on plasma concentrations of aspartate transaminase, alanine transaminase,  $\gamma$ -glutamyl transferase ( $\gamma$ -GT), alkaline phosphatase, or total cholesterol ( $P > 0.10$ ). Colostrum yield was positively correlated with urea ( $r = 0.50$ ;  $P = 0.01$ ) and creatinine ( $r = 0.43$ ;  $P = 0.03$ ) concentrations in sows on the day before farrowing. Mean litter BW gain over 2 wk was negatively correlated with concentrations of  $\beta$ -hydroxybutyric acid ( $r = -0.50$ ;  $P = 0.01$ ) and  $\gamma$ -GT ( $r = -0.42$ ;  $P = 0.03$ ) on the day before farrowing and was positively correlated with urea concentrations on the day before farrowing ( $r = 0.54$ ;  $P = 0.01$ ). In conclusion, at the dose of 12 g/d, silymarin did not influence prolactin concentrations or the hepatic status of sows, had no impact on colostrum production, and decreased litter BW gain in early lactation. Colostrum yield and litter performance during lactation were correlated with some markers of sow metabolic and hepatic status measured during the prepartum period.

**Key words:** colostrum, hepatic status, piglet performance, prolactin, silymarin, sow

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## INTRODUCTION

Lactogenesis is under hormonal regulation. The prepartum peak of prolactin in sows is essential for the synthesis of colostrum (Taverne et al., 1982; Farmer et al., 1998). Moreover, sows with a low colostrum yield tend to have a delayed increase in prolactin concentrations before farrowing (Foisnet et al., 2010). However, it is not known whether prolactin concentrations during the peripartum period influence colostrum production. In cows, hepatic disorders such as fatty liver can occur dur-

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ing the transition period (i.e., from late pregnancy to early lactation; Gerloff et al., 1986), and these disorders can be related to metabolic diseases, such as ketosis, which may have a detrimental effect on milk yield (Bobe et al., 2004). Whether sows are subject to liver and metabolic disorders during the peripartum period and whether these disorders affect colostrum and milk production is not clear yet. Silymarin, an extract from the plant *Silybum marianum*, increases milk yield in cows (Tedesco et al., 2004) and in women (Carotenuto and Di Pierro, 2005). Silymarin was also shown to increase prolactin concentrations in cyclic rats (Capasso et al., 2009). In gilts, providing silymarin from d 90 to 100 of pregnancy tended to increase prolactin concentrations (Farmer et al., 2014). Moreover, a preliminary test performed on 6 gilts showed that silymarin fed during the last 4 d of pregnancy increased circulating prolactin concentrations 24 h before farrowing (Loisel et al., 2013b). Silymarin is also widely known for its hepatoprotective properties and is used in humans for the treatment of liver diseases of different etiology (Saller et al., 2001). The present study therefore investigated the effects of silymarin intake during the last week of pregnancy on sow hormonal, hepatic, and metabolic status and determined whether relations exist between sow hepatic and metabolic status during the prepartum period and colostrum yield and piglet performances during lactation.

## MATERIALS AND METHODS

The study was conducted at INRA, Saint-Gilles, France. Animals were cared for according to the French regulations for the humane care and use of animals in research. The experimental protocol was approved by the local Ethics Committee in Animal Experiment of Rennes, France.

### Animals and Experimental Design

Thirty Landrace × Large White nulliparous sows were used in 5 replicates of 6 females. At approximately 285 d of age, sows were inseminated with semen from Piétrain boars. During pregnancy and until the day of farrowing, they were fed 2.5 kg of a conventional gestation diet daily (as-fed basis: 9.54 MJ of NE/kg, 13.3% CP, 0.6% lysine). Feed was provided in 2 equal meals at 0900 and 1500 h. Sows were moved from the gestation room to the farrowing room on d 105 of pregnancy (d 0 of pregnancy being the day of the first insemination) and were kept in individual farrowing crates thereafter. Stratified by their BW and back fat thickness, sows were then assigned to 1 of 2 experimental treatments and received either 12 g/d of silymarin (**SIL** sows,  $n = 15$ ) or no treatment (**Control** sows,  $n = 15$ ) from d 107 of pregnancy until the day of farrowing. Silymarin was a standardized milk thistle extract (Monteloeder, Elche, Spain). The extract contained

11.4% and 17.3% of silybin A and B, respectively (relative to the total milk thistle extract).

The SIL sows were fed 6 g of silymarin mixed with 25 mL of water and 300 g of gestation diet twice a day. The mixture was given to SIL sows before each meal, at the same time that Control sows received 300 g of the gestation diet without silymarin. After the intake of this silymarin mixture, sows were fed the rest of the meal (950 g of the gestation diet). On d 1 of lactation (d 0 of lactation being the day of farrowing), sows were fed 2.5 kg of a conventional lactation diet, providing 9.52 MJ of NE/kg, 17.5% CP, and 0.9% lysine (as-fed basis). Feed allowance during lactation was increased by 1 kg/d until ad libitum feeding, which was reached approximately on d 4 or 5 of lactation. From d 107 of pregnancy and throughout lactation, feed refusals were weighed daily, and actual feed intakes were calculated. During ad libitum feeding, feed troughs were filled twice a day, so that feed was always available. Water was freely available to sows throughout the experimental period. Sow water intake was recorded daily from d 107 of pregnancy until d 21 of lactation using individual water meters.

Fasted sows were weighed on d 101 of pregnancy and on d 2 and 21 of lactation. On those same days, back fat thickness was measured ultrasonically (Vetko plus, Noveko, Boucherville, QC, Canada) at the level of the 10th rib on each side, 65 mm from the midline. Farrowings were attended. Piglets were weighed at birth, 24 h after birth of the first piglet, and at 7, 14, and 21 d of age. Piglets had free access to water throughout lactation but had no access to creep feed. They were weaned at 21 d. Ambient temperature was maintained between 22°C and 25°C.

### Farrowing and Piglet Supervision during the First Day Postpartum

In order for treatment duration to be similar in all sows, parturition was induced on d 113 of pregnancy by an intramuscular injection of 2 mL of alfaprostol (Alfabédyl, Céva Santé Animale, Libourne, France). Such induction on d 113 was not expected to induce premature parturition (Foisnet et al., 2011). Farrowing duration was estimated as the time between the births of the first and the last piglets. The time that elapsed between birth and the first suckling was recorded for each piglet. When this latency exceeded 45 min, the piglet was placed on the dam to suckle. Piglets weighing less than 600 g at birth were euthanized immediately after birth. During the first 24 h postpartum, the original litter was kept with the sow. Beyond 24 h, litters were standardized to  $12 \pm 1$  piglets by cross-fostering within treatment group.



## Surgery and Sampling

**Surgery.** On d 105 of pregnancy, a catheter (2.16 mm o.d. and 1.02 mm i.d.; Silastic Dow Corning, Midland, MI) was inserted through a collateral vein in the right external jugular vein according to the protocol previously described by Loisel et al. (2013a).

**Blood Sampling.** Blood samples (15 mL) were collected from the fasted sows before feeding (0830 h) on d 107 and 109 of pregnancy, daily from d 111 of pregnancy until d 2 of lactation, and on d 7 and 21 of lactation. Additional blood samples (15 mL) were collected at 1630 and 0030 h from d 112 of pregnancy until the day after farrowing. Feed troughs were emptied at 2100 h the day before blood sampling. Blood samples were collected in heparinized (40 IU of heparin/mL) tubes (10 mL) or in tubes containing no anticoagulant (5 mL). Samples collected for plasma assays (heparinized tubes) were immediately centrifuged for 10 min at  $2,600 \times g$  at 4°C. Samples for serum assays were left at room temperature for 4 h, stored overnight at 4°C, and then centrifuged for 10 min at  $2,600 \times g$  at 4°C. Serum and plasma samples were frozen at -20°C until they were assayed.

**Postprandial Kinetics of Silybin A and B in Plasma.** On a subset of 6 SIL sows, serial blood samplings were performed for 24 h starting on the first day of the silymarin treatment (i.e., on d 107 of pregnancy). Blood samples were collected at -10 min (where time 0 corresponded to the first silymarin supply) and 1, 2, 3, 4, 5, 6, 8, 12, and 24 h. The last sampling was performed before the silymarin was supplied at 0900 h on d 108 of pregnancy. The duration of ingestion of the silymarin mixture was recorded for the 2 meals on d 107 of pregnancy.

**Colostrum and Milk Sampling.** Colostrum was collected immediately after birth of the first piglet (**T0**) and 24 h later (**T24**). Milk was collected on d 7 and 21 of lactation. At T24, colostrum was collected after an intramuscular injection of 20 IU of oxytocin (Oxytorem, Céva Santé Animale). On d 7 and 21 of lactation, milk was collected after an intravenous injection of 10 IU of oxytocin. Milk and colostrum samples (45 mL) were manually collected from several functional teats located in the anterior, middle, and posterior parts of the udder. They were immediately filtered through gauze and stored at -20°C.

## Biological Analyses

All hormonal and metabolite concentrations were determined in duplicate within single assays. The day of sampling was calculated in relation to the day of farrowing a posteriori.

**Silymarin Dose.** As silybin is the major active constituent of silymarin (Dixit et al., 2007; Hogan et al., 2007), the content of its two diastereoisomers A and B were analyzed in silymarin. The silybin A and B contents were as-

sayed using HPLC as described by Wen et al. (2008) by MasterLab Nutreco (Putten, The Netherlands). Briefly, 0.1 g of silymarin was mixed with 20 mL of methanol. The mixture was sonicated for 15 min at room temperature and diluted to 50 mL with methanol. The mixture was filtered and diluted with 50% methanol. Chromatographic analysis was performed using a Jasco AS-2055 autosampler (Jasco, Maarssen, The Netherlands), an Alltima C18 column (150 × 4.6 mm, 3 µm i.d.; Alltech, Breda, The Netherlands), and a Jasco UV-2075 detector. Silybin (Sigma Aldrich St. Louis, MO) was used as a standard.

**Silybin A and B Plasma Concentrations.** Silybin A and B concentrations were assayed in serial plasma samples as described by Wen et al. (2008) by MasterLab Nutreco. Briefly, 100 µL of plasma were hydrolyzed using a mixed enzyme solution containing sulfatase (EC 3.1.6.1, 80 U/mL) and β-glucuronidase (EC 3.2.1.3, 8,000 U/mL). Silybin A and B were then assayed by liquid chromatography - mass spectrometry using a Thermo Finnigan TSQ Quantum Discovery system with ESI probe (Thermo, San Jose, CA) and a Varian Microspher C18 column (50 × 4.6 mm, 3 µm i.d., Palo Alto, CA). Silybin (Sigma Aldrich, St. Louis, MO) was used as a standard, and naringenin was used as an internal standard (Sigma Aldrich). The limit of detection and linear quantitative range for silybin A and B were 2 to 1,000 and 5 to 1,000 ng/mL, respectively.

**Hormonal Assays.** Progesterone and prolactin concentrations were assayed in plasma and serum, respectively, on all single daily blood samples collected from d 107 of pregnancy until d 1 of lactation. Estradiol-17β, cortisol, and insulin were assayed in plasma samples collected before the morning meal on d 107 of pregnancy and from d -2 to 1 of lactation. Insulin was also assayed in additional samples collected before the morning meal on d 7 and 21 of lactation.

Plasma concentrations of progesterone, estradiol-17β, and insulin were measured by RIA using double-antibody commercial kits validated in pigs (product numbers IM1188 and A21854 for progesterone and estradiol-17β, respectively, Beckman Coulter, Roissy, France; Insulin-CT, Cisbio Bioassays, Codolet, France, for insulin). The intra-assay CV were 5.2%, 5.3%, and 4.7% and average sensitivity was 0.1 ng/mL, 6 pg/mL, and 3 µIU/mL for progesterone, estradiol-17β, and insulin, respectively. Serum prolactin concentrations were assayed using a homologous double-antibody RIA according to Robert et al. (1989). The intra-assay CV was 3.9%, and the sensitivity was 1.5 ng/mL. Plasma cortisol was measured using a fluorometric competitive enzyme immunoassay technique with the AIA-1800 Automated Immunoassay Analyzer (TOSOH Bioscience, Tokyo, Japan). The intra-assay CV and average sensitivity were 3.2% and 2 ng/mL, respectively.

**Enzyme and Metabolite Assays.** Plasmatic concentrations of glucose, NEFA, lactate, urea, creatinine, total

cholesterol,  $\beta$ -hydroxybutyric acid (**BHBA**), aspartate transaminase (**ASAT**; EC 2.6.1.1), alanine transaminase (**ALAT**; EC 2.6.1.2),  $\gamma$ -glutamyl transferase ( $\gamma$ -GT; EC 2.3.2.2), and alkaline phosphatase (**AP**; EC 3.1.3.1) were determined in single daily blood samples collected before the morning meal from d -2 to 1 of lactation and on d 7 and 21 of lactation. Automated enzymatic methods using an Automatic Analyzer (Konelab20i, Thermo, Cergy, France) employing commercial kits were used (product numbers 61269, 61192, 61162, 61218, 63212, 63312, 63712, 63609, bio-Mérieux, Marcy l'Etoile, France, for glucose, lactate, creatinine, total cholesterol, ASAT, ALAT,  $\gamma$ -GT, and AP, respectively; 754664, Wako, Dardilly, France, for NEFA; 07-3685-6, Roche, Neuilly-sur-Seine, France, for urea; and 984325, Thermo Fisher, Illkirch, France, for BHBA).

**Colostrum and Milk Composition.** Ash, DM, GE, CP, lipids, and lactose were assayed in colostrum at T0 and T24 and in milk on d 7 and 21 of lactation, as previously described by Loisel et al. (2013a). Immunoglobulins G (IgG) and A (IgA) were analyzed in colostrum at T0 and T24. Both IgG and IgA were analyzed by ELISA using commercial quantification kits for porcine IgG and IgA (references A100-104 and A100-102, respectively, Bethyl Laboratories, Montgomery, TX). Both IgG and IgA were assayed in triplicate. The intra- and interassay CV were, respectively, 2.9% and 7.0% for IgG and 4.0% and 5.8% for IgA.

#### Estimation of Colostrum and Milk Production

Individual colostrum intake by piglets was estimated from the piglet BW gain between birth and T24 according to the following equation developed in the present experimental herd (Devillers et al., 2004):  $CI = -217.4 + (0.217 \text{ ti}) + (1,861,019 \text{ BW}_{24}/\text{ti}) + \text{BWB} (54.8 - 1,861,019/\text{ti}) [(0.9985 - 3.7 \cdot 10^{-4} \text{ tFS}) + (6.1 \times 10^{-7} \text{ tFS}^2)]$ , where CI is individual colostrum intake (g), BWB is birth weight (kg), BW<sub>24</sub> is BW at T24 (kg), ti is the time that has elapsed between the first and the second weighing (min), and tFS is the interval between birth and the first suckling (min). Colostrum yield during the 24 h after the onset of farrowing was calculated as the sum of intakes by each piglet of the litter.

#### Statistical Analyses

Three Control sows were excluded from the experiment: 1 sow farrowed prematurely on d 111 of pregnancy, 1 sow exhibited poor maternal behavior, and 1 sow had impaired lactogenesis (colostrum yield < 1.5 kg). Data, except for mortality rate, were analyzed by ANOVA using the MIXED procedure (SAS Inst. Inc., Cary, NC). The sow or the litter represented the experimental unit in the model, which included the treatment (Control or SIL) as the main effect. Average litter size during the whole

lactation period was introduced as a covariate for piglet and litter performances during lactation. Time-related variations in concentrations of hormones, enzymes, and metabolites in blood were analyzed using repeated measures analyses. The model included the effects of treatment, sampling time, and the interaction. Colostrum or milk composition and IgG and IgA concentrations were analyzed within sampling day. Piglet mortality rate was analyzed using a logistic regression (GENMOD procedure), using a binomial error distribution with the treatment as a fixed effect. The link function was a logit transformation. Results of the logistic regression were then converted back to (original) natural units and expressed as means with confidence intervals. Pearson correlations were calculated between sow plasma concentrations of metabolites and enzymes prepartum (d -2 to d 0) and colostrum yield and litter performance to investigate the potential relationship between sow metabolic and hepatic status during the prepartum period and piglet performances during the colostrum and lactation periods. Values are expressed as means  $\pm$  SEM in text and figures.

## RESULTS

### Plasma Silybin A and B Concentrations after Silymarin Ingestion

The silymarin extract contained 28.7% silybin A and B. All sows ingested the feed and silymarin mixture within 5 min after delivery. Plasma concentrations of silybin A and B fluctuated over time ( $P < 0.05$ ; Fig. 1). They were below the limit of quantification 10 min before the first silymarin intake. Plasma silybin A concentrations increased ( $P < 0.05$ ) 1 h after the first silymarin intake, increased ( $P < 0.05$ ) again after the second feed-silymarin intake, and then gradually decreased ( $P < 0.05$ ). Plasma silybin B concentrations were highly variable among sows. They tended to increase 2 h after the first silymarin delivery ( $P < 0.10$ ), increased again, but not significantly, after the second delivery ( $P > 0.10$ ), and then decreased until 24 h ( $P < 0.05$ ).

### Sow Performance

Before the experiment, sow BW and back fat thickness on d 100 of pregnancy were similar in both treatment groups ( $P > 0.10$ ; Table 1) and averaged  $205.1 \pm 2.5$  kg and  $16.7 \pm 1.0$  mm, respectively. Sow BW and back fat thickness on d 2 and 21 of lactation were similar in both groups ( $P > 0.10$ ). Sow BW and back fat thickness lost between d 2 and 21 of lactation did not differ between groups ( $P > 0.10$ ).

From d 107 of pregnancy until farrowing, silymarin did not influence daily feed and water intakes of sows,

**Table 1.** Body weight, back fat thickness, and water and feed intakes for nulliparous sows fed 12 g/d of silymarin (SIL) or no treatment (Control) from d 107 of pregnancy until farrowing

Item	Groups		SEM <sup>1</sup>	P-value
	Control	SIL		
No. of sows	12	15		
BW, kg				
d 100 of pregnancy	204.6	205.5	2.5	0.76
d 2 of lactation	190.2	193.1	2.8	0.45
d 21 of lactation	176.2	183.1	4.2	0.16
Loss between d 2 and 21 of lactation	14.0	10.0	2.5	0.23
Back fat thickness, mm				
d 100 of pregnancy	16.8	16.6	1.0	0.90
d 2 of lactation	17.2	17.5	1.1	0.58
d 21 of lactation	14.6	15.3	1.0	0.36
Loss between d 2 and 21 of lactation	2.6	2.1	0.7	0.49
Average water intake, L/d				
d 107 to farrowing	14.9	18.9	2.5	0.31
wk 1 of lactation	18.6	22.1	2.3	0.33
wk 2 of lactation	24.5	29.4	2.2	0.10
wk 3 of lactation	25.0	30.7	3.0	0.23
Average feed intake, kg/d				
d 107 to farrowing	2.40	2.45	0.10	0.58
wk 1 of lactation	4.09	4.28	0.30	0.54
wk 2 of lactation	5.79	5.90	0.33	0.78
wk 3 of lactation	5.68	5.81	0.37	0.88

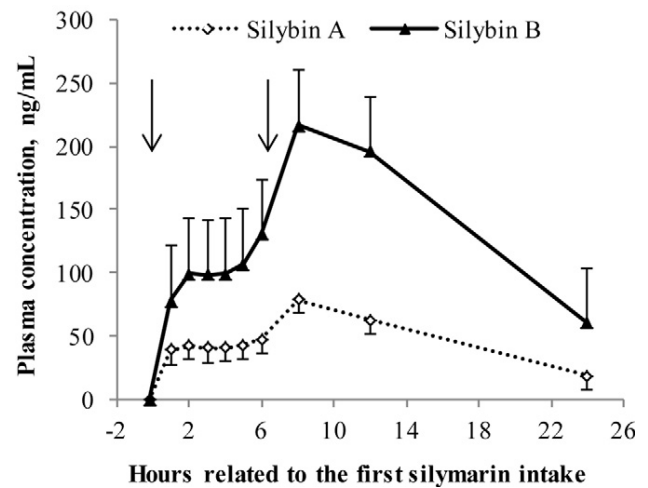
<sup>1</sup>Maximal SEM.

which averaged  $2.43 \pm 0.07$  kg/d and  $16.8 \pm 3.4$  L/d, respectively ( $P > 0.10$ ). Average feed intake and water consumption during lactation did not differ between treatments ( $P > 0.10$ ; Table 1).

Pregnancy and farrowing durations were not influenced by treatment ( $P > 0.10$ ; Table 2). Average pregnancy duration (113.8 d) was close to pregnancy duration recorded for gilts in the absence of induction in the present experimental herd (114.2 d; Foisnet et al., 2011). The average interval between births was similar in both groups ( $P > 0.10$ ).

#### Litter Characteristics during the First 24 h and Colostrum Yield

Litter size at birth and T24 did not differ in the two treatments ( $P > 0.10$ ; Table 2). Treatment did not influence mean BW at birth or at T24 or mean BW gain of piglets during the first 24 h ( $108 \pm 18$  and  $107 \pm 14$  g for Control and SIL sows, respectively;  $P > 0.10$ ). Silymarin treatment did not influence ( $P > 0.10$ ) birth to suckling interval, average colostrum intake by piglets, or estimated colostrum yield (Table 2). The mortality rate of piglets between birth and T24 was 8.4% [4.9%, 13.9%] and 4.3% [2.2%, 8.4%] in litters from Control and SIL sows, respectively ( $P > 0.10$ ).



**Figure 1.** Profiles of plasma concentrations of silybin A and B in 6 SIL sows after silymarin consumption on d 107 of pregnancy. Arrows indicate time of silymarin intake by the sows. Error bars represent the SEM. SIL sows were fed 12 g/d of silymarin from d 107 of pregnancy until the day of farrowing.

#### Performances during Lactation

Litter sizes on d 1 (after cross-fostering) and on d 21 of lactation were similar in both groups ( $P > 0.10$ , Table 3). Piglet mortality from d 1 to 21 of lactation was not influenced by treatment and averaged 12.1% [7.7%, 18.7%] and 8.5% [5.2%, 13.7%] in litters from Control and SIL sows, respectively ( $P > 0.10$ ). Mean piglet BW was similar on d 1 but lower on d 7, 14, and 21 of lactation for piglets born from SIL sows compared with piglets born from Control sows ( $P < 0.05$ ). Average litter BW gain was lower on wk 1 ( $P < 0.05$ ) in litters born from SIL sows compared with litters from Control sows.

#### Colostrum and Milk Composition

DM, ash, lipid, protein, lactose, and GE in colostrum and in milk were not influenced by treatment ( $P > 0.10$ ; data not shown). IgG and IgA concentrations in colostrum averaged, respectively,  $42.0 \pm 7.5$  and  $7.9 \pm 0.6$  mg/mL at T0 and  $15.4 \pm 0.4$  and  $3.8 \pm 0.4$  mg/mL at T24. They were not influenced by treatment ( $P > 0.10$ ).

#### Sow Endocrine and Metabolic Status

**Hormones.** Silymarin did not influence ( $P > 0.10$ ) circulating concentrations of prolactin in sows (Fig. 2). Profiles of all hormones fluctuated over time ( $P < 0.001$ ) but were not influenced by treatment ( $P > 0.10$ ). The sampling time by treatment interaction was not significant ( $P > 0.10$ ).

**Metabolites.** From d 111 of pregnancy until d 21 of lactation, preprandial concentrations of NEFA, lactate, and creatinine fluctuated over time ( $P < 0.001$ ) without treatment effect or sampling time by treatment interaction ( $P > 0.10$ ; data not shown). For glucose, the



**Table 2.** Piglet and litter characteristics and colostrum production during the first 24 h postpartum for nulliparous sows fed 12 g/d of silymarin (SIL) or no treatment (Control) from d 107 of pregnancy until farrowing

Item	Group		SEM <sup>1</sup>	P-value
	Control	SIL		
No. of sows	12	15		
Pregnancy length, d	113.8	113.7	0.2	0.48
Farrowing duration, min	165.1	155.1	24.7	0.75
Average interval between births	13.6	12.5	2.1	0.70
Litter size at birth				
Total born	13.1	12.6	0.8	0.58
Born alive	12.9	12.3	0.8	0.56
Litter birth weight, <sup>2</sup> kg	15.4	15.0	0.79	0.69
Mean piglet BW, <sup>2</sup> kg				
At birth	1.24	1.25	0.07	0.68
At T24 <sup>3</sup>	1.36	1.36	0.08	0.68
Colostrum intake by individual piglets, g	318	312	28	0.91
Litter BW gain between birth and T24, kg	1.24	1.21	0.16	0.96
Birth to suckling interval, min	30	29	2	0.36
Colostrum production between T0 and T24, <sup>4</sup> kg	3.7	3.6	0.3	0.79

<sup>1</sup>Maximal SEM.<sup>2</sup>Piglets born alive.<sup>3</sup>T24 = 24 h after the onset of parturition.<sup>4</sup>T0 = onset of parturition.

sampling time by treatment interaction was significant ( $P < 0.05$ ; Fig. 3). Plasma glucose concentrations tended to be lower on the day of farrowing and greater on d 1 of lactation in SIL compared with Control sows ( $P < 0.10$ ). For BHBA, neither treatment nor treatment by sampling time interaction was significant ( $P > 0.10$ ; Fig. 4). Plasma concentrations of BHBA were lower ( $P < 0.05$ ) on d 0 than on d -2 and -1 and were greater ( $P < 0.05$ ) on d 7 of lactation than on d 1 and on d 21 than on d 7.

**Sow Hepatic Status.** Plasma concentrations of ASAT, ALAT,  $\gamma$ -GT, AP, and total cholesterol were not influenced by the treatment ( $P > 0.10$ ; Fig. 5). For all the variables measured, there was an overall time effect ( $P < 0.001$ ). Plasma concentrations of ASAT decreased ( $P < 0.05$ ) from d -2 to -1, increased ( $P < 0.05$ ) progressively from d -1 to 1, and then decreased ( $P < 0.05$ ) from d 1 to 7 of lactation (Fig. 5a). Plasma concentrations of ALAT decreased ( $P < 0.05$ ) from d -2 to -1, increased ( $P < 0.05$ ) from d -1 to 0, and decreased from d 1 to 7 of lactation (Fig. 5b). Plasma concentrations of  $\gamma$ -GT increased from d -2 to 0 and decreased ( $P < 0.05$ ) progressively from d 0 to 7 of lactation (Fig. 5c). Plasma concentrations of AP decreased ( $P < 0.05$ ) from d -2 to -1, increased ( $P < 0.05$ ) from d -1 to 0, decreased ( $P < 0.05$ ) from d 0 to 7 of lactation, and increased ( $P < 0.05$ ) from d 7 to 21 of lactation (Fig. 5d). Plasma concentrations of total cholesterol decreased ( $P < 0.05$ ) gradually from d -1 to 1

**Table 3.** Piglet and litter performance during lactation for nulliparous sows fed 12 g/d of silymarin (SIL) or no treatment (Control) from d 107 of pregnancy until farrowing

Item	Groups		SEM <sup>1</sup>	P-value
	Control	SIL		
No of sows	12	15		
Litter size				
d 1	11.7	11.7	0.6	0.79
d 21	10.3	10.7	0.5	0.37
Mean piglet BW, kg				
d 1 <sup>2</sup>	1.36	1.36	0.08	0.81
d 7 <sup>3</sup>	2.58	2.41	0.09	0.01
d 14 <sup>3</sup>	4.45	4.13	0.12	0.01
d 21 <sup>3</sup>	6.39	5.97	0.17	0.02
Mean piglet BW gain, <sup>4</sup> g/d				
Between d 1 and 7	196	171	5	0.01
Between d 7 and 14	263	236	11	0.05
Between d 14 and 21	273	261	12	0.41
Litter BW gain, <sup>4</sup> kg/d				
Between d 1 and 7	2.05	1.90	0.10	0.03
Between d 7 and 14	2.73	2.55	0.16	0.10
Between d 14 and 21	2.78	2.80	0.13	0.48
Between d 1 and 21	2.41	2.35	0.11	0.11

<sup>1</sup>Maximal SEM.<sup>2</sup>After cross-fostering.<sup>3</sup>Mean piglet BW on d 1 was used as a covariate.<sup>4</sup>Average litter size during lactation was introduced as a covariate.

and then increased ( $P < 0.05$ ) progressively from d 1 to 21 of lactation (Fig. 5e).

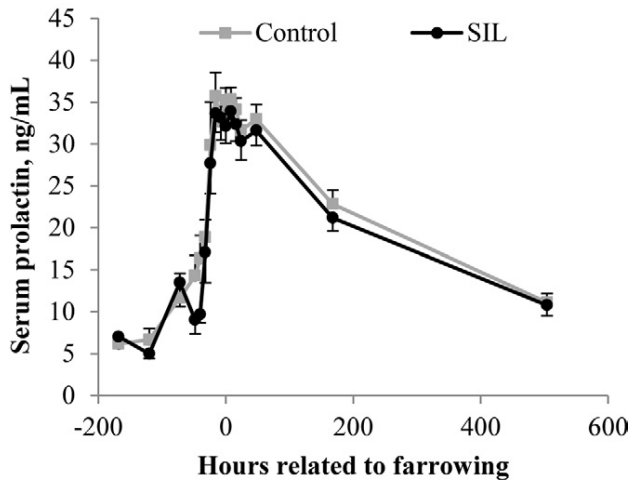
#### Relations between Sow Metabolic and Hepatic Status Prepartum and Colostrum Yield and Litter Growth

Colostrum yield and mean litter BW gain from birth to T24 and during lactation were not correlated with ASAT, ALAT, AP, glucose, lactate, and NEFA concentrations at any sampling time prepartum ( $P > 0.10$ ; data not shown).

**Colostrum Yield.** Colostrum yield was positively correlated with urea ( $P = 0.01$ ; Table 4) and creatinine ( $P = 0.03$ ) concentrations on d -1 but was not correlated with concentrations of other metabolites and enzymes ( $P > 0.10$ ; Table 4).

**Litter Performance during Lactation.** Mean litter BW gain during the first week of lactation was positively correlated ( $P = 0.02$ ) with urea concentrations in sows on d -1 and negatively correlated ( $P = 0.01$ ) with BHBA concentrations on d -1 of lactation but was not correlated with hepatic enzyme concentrations ( $P > 0.10$ ; Table 4). Mean litter BW gain during the first 2 wk of lactation was positively correlated ( $P = 0.01$ ) with urea concentrations in sows on d -1 and negatively correlated with BHBA ( $P = 0.01$ ) and  $\gamma$ -GT ( $P = 0.03$ ) on d -1. When considering litter BW gain during the whole lactation,



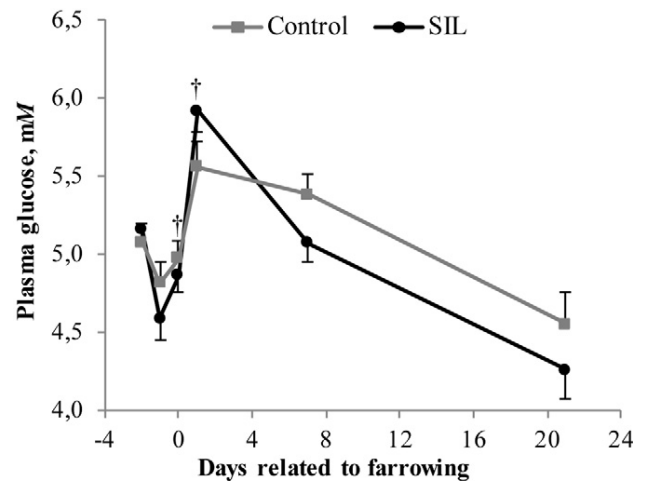


**Figure 2.** Serum prolactin concentrations for sows fed 12 g/d of silymarin (SIL) or no treatment (Control) from d 107 of pregnancy until the day of farrowing. Error bars represent the SEM.

the correlations with urea and  $\gamma$ -GT on d -1 were only tendencies ( $P = 0.05$ ), and the correlation with BHBA was still highly significant ( $P = 0.01$ ).

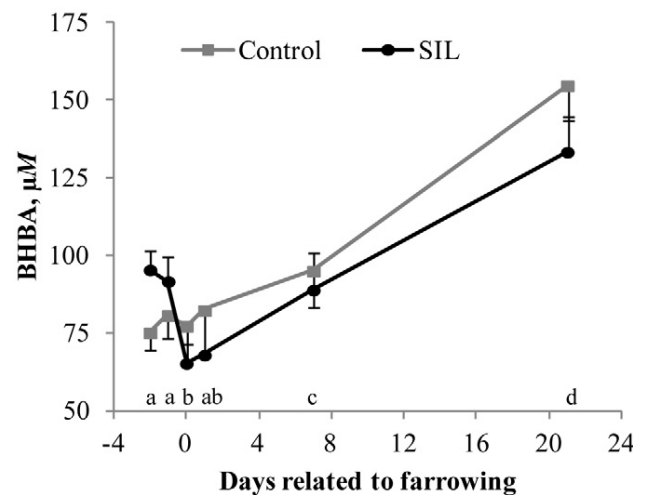
## DISCUSSION

In the present study, supplying 12 g/d of silymarin to gilts during the last 8 d of pregnancy did not increase circulating concentrations of prolactin. At a dose of 8 g/d, silymarin was shown to increase prolactin concentrations when provided to gilts from d 90 to 100 of pregnancy ( $P < 0.10$ ; Farmer et al., 2014) or from d 111 of pregnancy until the day of farrowing ( $P < 0.05$ ; Loisel et al., 2013b). The lack of effect of silymarin on prolactin concentrations in the current study remains unexplained. Silymarin is a complex of flavonoids, and silybin is its major active and abundant constituent (Dixit et al., 2007; Hogan et al., 2007). The silymarin extract used by Farmer et al. (2014) and Loisel et al. (2013b) contained concentrations of silybin similar to the extract used in the present study (26.7% vs. 28.7%). Moreover, the increase in silybin A and B concentrations in the plasma of SIL sows indicated that silybin was absorbed at the level of the gastrointestinal tract. Furthermore, silymarin influenced sow plasma glucose concentrations during the prepartum period, indicating that in the present study it was biologically active. The possibility that the lack of effect of silymarin on prolactin could be related to a difference in concentrations of the other flavonoids composing silymarin or to a lower bioavailability of flavonoids in the extract used in the present study cannot be ruled out. Progesterone, estradiol-17 $\beta$ , and cortisol are likely to be involved in the regulation of colostrum production, along with prolactin, yet they were not affected by silymarin.

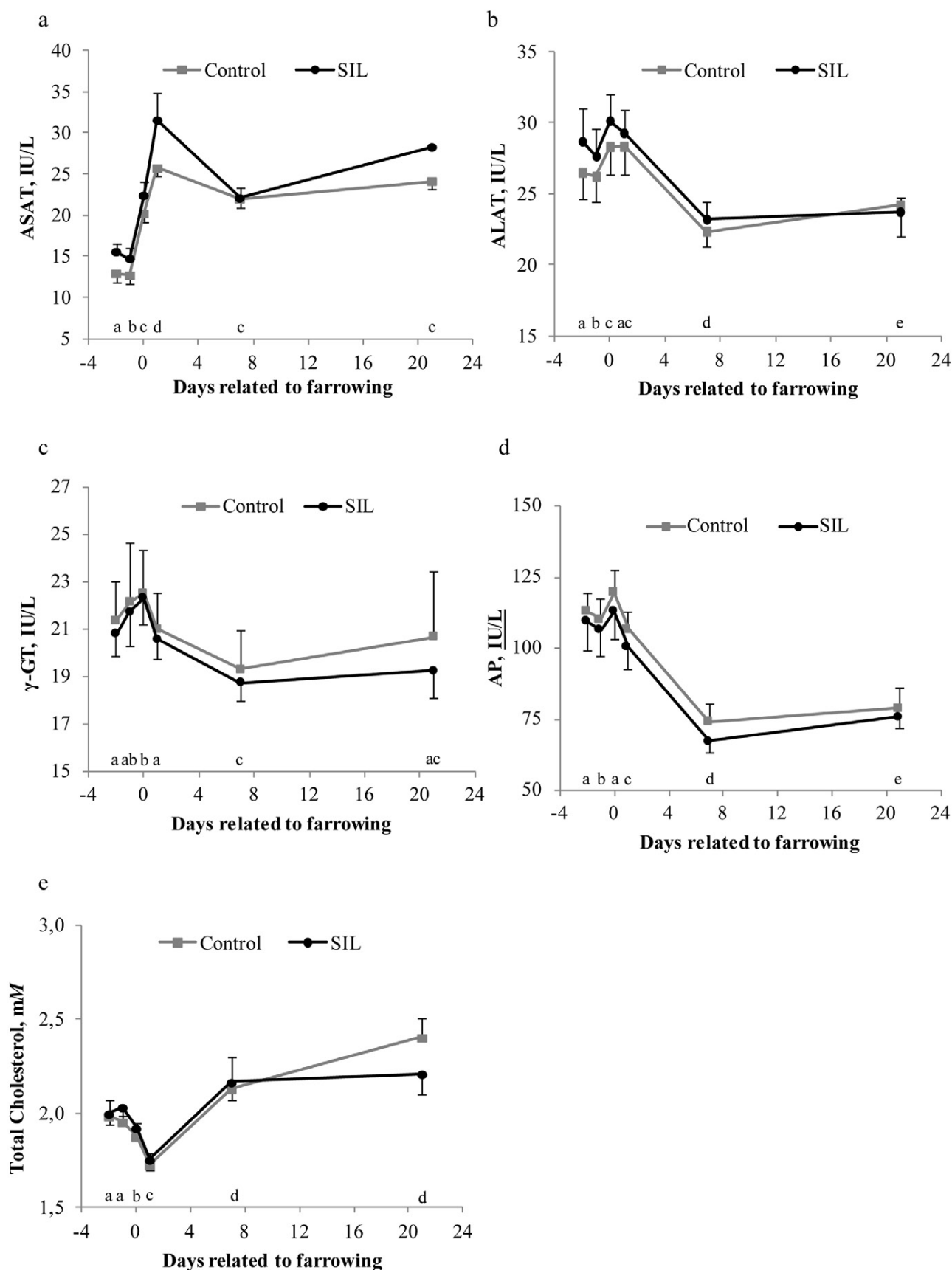


**Figure 3.** Preprandial concentrations of plasma glucose for sows fed 12 g/d of silymarin (SIL) or no treatment (Control) from d 107 of pregnancy until the day of farrowing. Significant sampling by treatment interaction ( $P < 0.05$ ). †Treatment effect ( $P < 0.10$ ). Error bars represent the SEM.

Silymarin administration in this study did not influence plasma concentrations of hepatic enzymes or cholesterol. These results are in agreement with those from Tedesco et al. (2004), where, in cows, silymarin treatment during late pregnancy and the beginning of lactation did not influence  $\gamma$ -GT or cholesterol concentrations. These authors specified that the cows used in their study did not present serious liver damage. In contrast, in rats presenting ethanol-induced liver damage, silymarin intake decreased  $\gamma$ -GT, ASAT, ALAT, and AP concentrations (Wang et al., 1996). Moreover, the polyphenolic fraction of silymarin counteracts the development of steatosis in rats (Skottova et al., 2003), the severity of which can be evaluated using ASAT, ALAT, or  $\gamma$ -GT plasma concentrations as markers of serious hepatic dysfunction or damage (Ohtsuka et al.,



**Figure 4.** Preprandial concentrations of plasma of  $\beta$ -hydroxybutyric acid (BHBA) for sows fed 12 g/d of silymarin (SIL) or no treatment (Control) from d 107 of pregnancy until the day of farrowing. Time effect: sampling times with different letters differ ( $P < 0.05$ ). Error bars represent the SEM.



**Figure 5.** Preprandial plasma concentrations of (a) aspartate transaminase (ASAT), (b) alanine transaminase (ALAT), (c)  $\gamma$ -glutamyl transferase ( $\gamma$ -GT), (d) alkaline phosphatase (AP), and (e) total cholesterol for sows fed 12 g/d of silymarin (SIL) or no treatment (Control) from d 107 of pregnancy until the day of farrowing. Time effect: sampling times with different letters differ ( $P < 0.05$ ). Error bars represent the SEM.

**Table 4.** Correlations between colostrum yield and litter BW gain during lactation and some markers of sow hepatic and metabolic status<sup>1,2</sup>

Item <sup>3</sup>	Colostrum yield	Mean litter BW gain during lactation		
		d 1 to 7	d 1 to 14	d 1 to 21
Urea on d -1	$r = 0.50, P = 0.01$	$r = 0.45, P = 0.02$	$r = 0.54, P = 0.01$	$r = 0.39, P = 0.05$
Creatinine on d -1	$r = 0.43, P = 0.03$	$r = -0.13, P = 0.53$	$r = -0.15, P = 0.48$	$r = -0.12, P = 0.55$
BHBA on d -1	$r = -0.12, P = 0.57$	$r = -0.51, P = 0.01$	$r = -0.50, P = 0.01$	$r = -0.52, P = 0.01$
$\gamma$ -GT on d -1	$r = -0.11, P = 0.58$	$r = -0.28, P = 0.17$	$r = -0.42, P = 0.03$	$r = -0.38, P = 0.05$

<sup>1</sup>Pearson's correlations.<sup>2</sup>Note d 0 of lactation is the day of farrowing.<sup>3</sup>BHBA =  $\beta$ -hydroxybutyric acid;  $\gamma$ -GT =  $\gamma$ -glutamyl transferase.

2001). To the best of our knowledge, the present study is the first to report the evolution of plasma concentrations of hepatic enzymes in sows during the peripartum period. Plasma concentrations of  $\gamma$ -GT and ASAT observed at d 112 of pregnancy in the present study were within the range reported for nulliparous sows at  $108 \pm 2$  d of gestation (Verheyen et al., 2007), whereas AP concentrations were greater in the present study. Nevertheless, it is not possible to determine whether the greater concentrations of hepatic enzymes seen before or at parturition compared with concentrations observed during lactation are linked to hepatic dysfunction. It cannot be ruled out that silymarin had no impact on hepatic enzyme concentrations in the present experiment because the sows did not present severe hepatic dysfunction.

Silymarin had little influence on sow metabolic state. Silymarin only influenced glucose concentrations during the peripartum period. This finding is in agreement with previous reports whereby silymarin exhibited potent effects on glucose metabolism in rats and humans (Maghrani et al., 2004; Vellusi et al., 1997). The silymarin effect on glucose concentrations had no consequences on colostrum and milk yield and composition, although plasma glucose is the major precursor for the synthesis of colostrum/milk constituents. Silymarin treatment did not influence sow plasma BHBA concentrations. In cows, the effect of silymarin on BHBA concentrations is controversial, showing no effect (Tedesco et al., 2004) or a decrease (Vojtisek et al., 1991). Ketone bodies, such as BHBA, are indicators of ketosis (Nielsen et al., 2005). Discrepancies between studies could be related to the severity of ketosis at the onset of silymarin treatment. Whether sows in the present experiment suffered from ketosis cannot be determined because of the lack of reference values in sows. Nevertheless, the lower concentrations of BHBA at farrowing compared with during lactation suggested the absence of severe ketosis during the treatment period, which could explain the lack of silymarin effect on plasma BHBA concentrations.

Few studies have reported plasma concentrations of BHBA during pregnancy and lactation in sows. In the present study, mean concentrations increased during

lactation and were greater during lactation than before farrowing. Revell et al. (1998) reported greater plasma concentrations of BHBA in wk 2 of lactation compared with concentrations before farrowing but also compared with concentrations in wk 4 of lactation. Recently, Theil et al. (2013) reported BHBA concentrations in sows to be greatest 1 wk before farrowing, lowest 3 d before farrowing, and intermediate during lactation. Ketone bodies are synthesized in the liver when glucogenic substrates are insufficient and fat oxidation is prevalent. During lactation, glucogenic substrates are largely used by the mammary gland for milk synthesis, and sows, especially first-parity sows, experience body lipid mobilization. The increase in BHBA concentrations during lactation in the present study is consistent with such adaptations. Variability of BHBA profiles among studies may originate from the composition of diets during lactation and the energy balance of sows (i.e., energy intake related to energy requirement to sustain milk production).

In the present experiment, plasma concentrations of BHBA in sows on d -1 were negatively correlated with mean litter BW gain at different stages of lactation, suggesting a negative relation between BHBA concentrations before parturition and sow milk yield. However, whether this correlation reflects a causal relation is not known. The SIL sows exhibited greater concentrations of BHBA before farrowing than the Control sows, although the difference was not significant, and their litters grew slower during wk 1 of lactation than litters from Control sows. Moreover, plasma concentrations of  $\gamma$ -GT the day before farrowing were negatively correlated with litter BW gain during lactation, especially during the first 2 wk. Collectively, these findings suggest a relation between sow hepatic status before parturition and lactational performance.

Plasma concentrations of creatinine and urea the day before farrowing were positively correlated with colostrum yield. Urea is the final metabolite derived from dietary protein and tissue protein turnover. Creatinine is an indicator of lean body mass of the sow (Baxmann et al., 2008). These correlations suggest that protein metabolism during the prepartum period could influence lac-



togenesis in sows and, more specifically, that a greater lean mass or a greater body protein loss during the prepartum period or both could be related to sow lactational performance immediately after farrowing. In sows, a high rate of colostrum synthesis occurs during the hours preceding farrowing (Theil et al., 2014). Sow body protein can be used by the mammary glands as a source of amino acids or glucogenic substrates (Theil et al., 2012). Thus, a greater body protein mobilization during the day before farrowing may be associated with an increased synthesis of colostrum constituents and therefore an increased colostrum yield. However, Decaluwé et al. (2013) used (iso)butyrylcarnitine as a marker of body protein catabolism and reported a negative correlation between its serum concentrations 3 to 4 d before farrowing and colostrum yield. Discrepancies between the two studies may originate from the metabolic status of the sows during the prepartum period. Indeed, in the present study, sows were in an anabolic status, whereas in the study of Decaluwé et al. (2013) sows were catabolic. Excessive catabolism may have a detrimental effect on colostrum yield. In the present study, plasma concentrations of urea on d -1 were also positively correlated with litter BW gain at different stages during lactation. The potential relation between sow protein metabolism during late gestation and lactational performance warrants further investigation.

In conclusion, providing silymarin to sows during the last week of pregnancy did not influence circulating prolactin concentrations, hepatic status, or colostrum production or piglet weight gain until weaning. Correlations suggested that colostrum yield could be influenced by prepartum sow protein metabolism. Furthermore, negative correlations found between litter BW gain during the first 2 wk of lactation and BHBA and  $\gamma$ -GT concentrations before farrowing suggested that hepatic status and ketone body formation during the peripartum period could have detrimental effects on sow lactational performance.

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