Metabolites of vitamin D and minerals in blood and colostrum of primiparous and multiparous dairy cows postpartum

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ABSTRACT: Concentrations of calcidiol, calcitriol, and minerals in blood serum and colostrum of 14 primiparous and 16 multiparous Holstein dairy cows during short-period prepartum and postpartum were determined and compared. Blood samples were collected between days 5 and 2 prepartum and 6 h, 12 h, 7 and 21 days postpartum. Nearly 66% of primiparous and 71% of multiparous cows had subclinical postpartum hypocalcemia. Prepartum serum calcium (Ca) and inorganic phosphorus (P) were higher in primiparous cows; Ca decreased in both groups at 6 and 12 h and returned to baseline values 7 days postpartum. Calcidiol and calcitriol concentrations were equal on day 5 prepartum in both groups. In multiparous cows, calcidiol and calcitriol concentration increased at 6 h postpartum and remained elevated at 12 h postpartum; there were no changes in primiparous cows for these analytes. The total secretion of Ca in the colostrum from the first milking was similar in both groups and positively correlated with serum Ca at 6 and 12 h after calving. It is concluded that postpartum increases in the calcidiol and calcitriol concentration were a normal response to the decrease of serum calcium concentration only in multiparous cows. The total Ca secretion in the colostrum of the first milking postpartum does not reflect the grade of hypocalcemia.

Keywords: calcidiol; calcitriol; calcium; peripartum cow

Subclinical hypocalcemia (Ca < 2.0 mmol/l without clinical signs) occurs in more than 60% of multiparous and 25% of primiparous cows during the first 24 h after calving (Goff, 2008). The incidence of subclinical hypocalcemia increases with the number of calving in cows (Reinhardt et al., 2011). This coincides with the beginning of the colostrum secretion, which suddenly increases the Ca demand (Goff, 1999). When serum Ca decreases, the parathyroid gland increases secretion of parathormone (PTH) (Capen and Young, 1967). The PTH acts on kidney, increasing the tubular reabsorption of Ca into the blood and stimulates production of 1α-hydroxylase, which converts calcidiol (25(OH) D_3) to calcitriol (1,25$(OH)_2$ D_3). Calcitriol is the active form of vitamin D that increases the intestinal absorption of Ca, while the PTH removes Ca deposited in bones and increases its serum concentration (Goff, 1999).

In humans, some hepatic diseases like cirrhosis or hepatic lipidosis decrease the activity of 25-hydroxylase enzyme, which affects the production

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of calcidiol (Lalor et al., 1986). The decline in dry matter intake and the beginning of milk synthesis during the transition period increase the energy requirements for the female, so the cow goes into a negative energy balance (Aparicio-Cecilio et al., 2012). Lipids stored in adipocytes are mobilized in the form of non-esterified fatty acids (NEFA) and glycerol to the liver in order to meet the new demands for energy. In liver, NEFA can enter the tricarboxylic acid cycle, be converted to ketones or be re-esterified and accumulate in hepatic tissues as triglycerides (Drackley et al., 2001). Dairy cows with body condition score (BCS) ≥ 4 have a higher risk of becoming hypocalcemic. These cows decrease consumption of dry matter before calving and fall into a state of negative energy balance; therefore serum concentration of NEFA and liver triglyceride accumulation are greater than in primiparous cows (Van de Haar et al., 1999). This could adversely affect the hepatic synthesis of calcidiol and be a predisposing factor for hypocalcemia in multiparous cows. Our hypothesis was that postpartum hypocalcemia may be primarily related to metabolic alterations of calcidiol and calcitriol and in a lesser extent to metabolic alterations of P, Mg, NEFA, β-hydroxybutyrate (BHBA), and the amount of Ca in colostrum. The aim of this study was to determine and compare primiparous and multiparous cows regarding serum calcidiol, calcitriol, Ca, P, Mg, NEFA, BHBA, and the amount of Ca that is secreted by colostrum and their correlations as a qualitative cause of postpartum hypocalcemia.

MATERIAL AND METHODS

Animals and treatments. This study was conducted in a commercial large farm of 2600 Holstein dairy cows with an average annual milk production of 7930 kg/cow, near the city of Torreon, Coahuila, Mexico. All experimental techniques and procedures were approved by the Subcommittee for Investigation and Care of Animals in Experimentation of the Veterinary Faculty and Husbandry of the National Autonomous University of Mexico. 5–2 days before the expected date of calving, 16 multiparous and 14 primiparous cows were selected with a BCS between 3.25 and 3.75 points (1–5 scale; Ferguson et al., 1994). Cows received a prepartum integral diet (Table 1) and water *ad libitum*, and were kept under observation until calving. All animals were moved to another pen, then were milked completely, and offered a postpartum diet (Table 1) *ad libitum.* As an established management procedure, only the multiparous cows received 500 ml of Ca borogluconate (25%) via intravenous injection (Cal Mag K; Bimeda de Mexico SA de CV, Queretaro, Mexico), starting at 6 h and after the first postpartum blood sampling.

During the first 15 days, animals were evaluated by a clinical examination and their health status was recorded between 8:00 and 10:00 h. The experimental design consisted of an observational prospective study with repeated measurements.

Table 1. Ingredients and chemical composition of prepartum and postpartum diets (in %)

Ingredient	Prepartum	Postpartum
Alfalfa hay	10.61	4.66
Ground corn	12.38	17.76
Corn bran	0.71	–
Soybean meal	0.35	–
Oat hay	3.54	–
Corn silage	70.76	43.13
Water	–	10.15
Alfalfa silage	–	5.82
Cottonseed meal	–	5.08
Sugarcane molasses	–	3.81
Cotton seed	–	2.54
Canola meal	–	5.08
Vitamin and mineral premix	1.65	1.97
Chemical composition		
Moisture (%)	55.46	50.85
CP (%)	11.54	16.75
NDF (%)	36.93	34.68
NE_L (Mcal/kg)	1.45	1.54
Ca (%)	0.81	0.78
P (%)	0.39	0.37
Mg (%)	0.15	0.23
Na (%)	0.09	0.29
K (%)	1.30	1.27
Cl (%)	0.36	0.37
S (%)	0.43	0.46
Vitamin D (UI/kg)	1980	2364
DCAD (meq/100 g DM)	0.2	5.9

CP = crude protein, NDF = neutral detergent fibre, NE_L = net energy for lactation, DCAD = difference cation anion of diet, DM = dry matter

The independent variables were group and time regarding calving. The dependent variables were the serum concentrations of calcidiol, calcitriol, Ca, P, Mg, NEFA, BHBA, and Ca secreted in colostrum.

Sampling and analyses. Samples of the prepartum and postpartum ration were taken directly into plastic bags and stored at –20°C until analysis. Blood samples were taken from all cows by the tail vein puncture in 7 ml vacuum tubes without anticoagulant (Monoject®; Argtech Inc., Manhattan, USA) between 5 and 2 days before the estimated calving date, at 6 h postpartum (after the first milking), 12 h, 7 and 21 days after calving. Blood samples were centrifuged within 1 h after sampling at 1200 *g* for 10 min. The serum samples and colostrum from the first postpartum milking (10 ml) were placed into plastic vials and stored at –20°C until analysis.

Humidity percentage, acid and neutral detergent fibre, Ca, Mg, Na, and K were determined in ration samples by atomic absorption spectrophotometry (SpectrAA 50; Varian Australia Pty. Ltd., Mulgrave, Australia); P was assessed by a colourimetric method (AOAC, 1984). Serum calcidiol concentration was determined by a chemiluminescent method (Liasion; DiaSorin, Stillwater, USA). Calcitriol was measured by radioimmunoassay (Hollis, 1986), with a commercial reagent (DiaSorin). Serum Ca, P, Mg, NEFA, and BHBA were determined using commercial kits (Randox Laboratories Ltd., Crumlin, UK) in a semi-automatic analyzer (model Selectra Junior; Vital Scientific, Spankeren, the Netherlands). Concentration of Ca in colostrum was determined using atomic absorption spectrophotometer Perkin Elmer, model 3110 (Perkin Elmer, Norwalk, USA) (AOAC, 1984).

Statistical analysis. Serum concentrations of the analytes were evaluated by the Analysis of Variance for repeated measurement design in a General Linear Model in the statistical program SPSS (Version 10.01, 1999). The model included the group effect, time regarding calving, and time × group interaction. The assumption of homogeneity of variances was verified using the Levene and sphericity of covariance test through out the Mauchly test (Diggle, 1988). When this assumption was not met, the statistical decision was based on Wilks' lambda multivariate statistic approximate by *F* Multiple comparisons adjusted by the Bonferroni test, aiming to assess the main effects (Diggle, 1988). The amount of Ca in colostrum was analyzed by using the Student's *t*-test. Significant statistical difference was considered when the *a* value was lower than 0.05; thus level of significance will not be informed about in this work when it adjusts to this criterion, otherwise it will be indicated. Pearson's correlation test was used to examine the relationship among values of the studied variables; the criterion for statistical difference was $a < 0.05$.

RESULTS

At 5–2 days before calving, serum Ca concentration was higher in primiparous than in multipa-

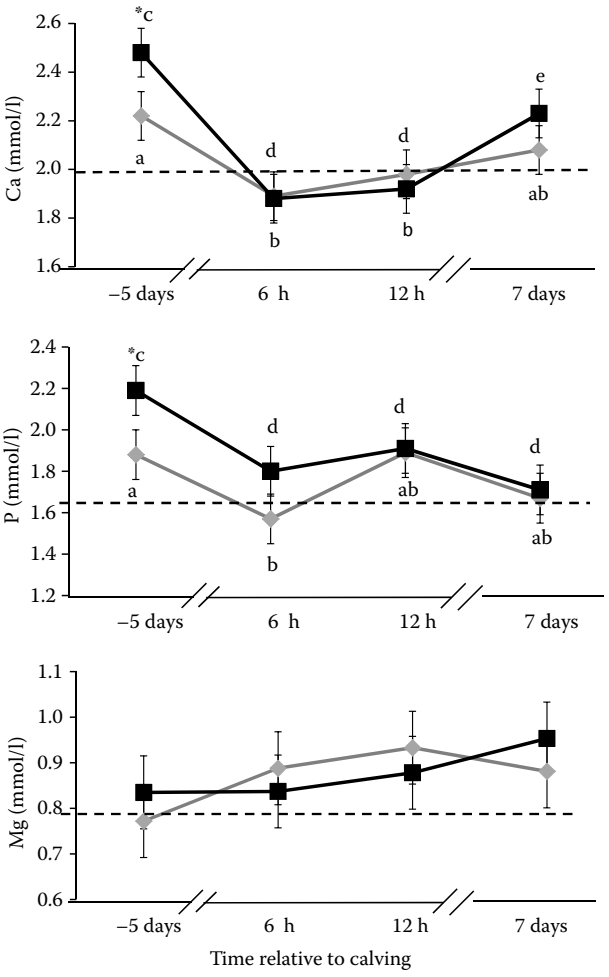

Figure 1. Serum concentrations of calcium (Ca), phosphorus (P), and magnesium (Mg) in multiparous (◆; $n = 16$) and primiparous (■; $n = 14$) dairy cows before and after calving (mean ± SD)

means with different letters (a, b – multiparous cows, c–e – primiparous cows) differ significantly ($P < 0.05$)

*significant difference ($P < 0.05$) between multiparous and primiparous cows at the same sampling time

----- lower value of the reference interval (Goff, 2008)

rous cows but in all samples taken postpartum no difference between groups was found (Figure 1). Relative to prepartum values, Ca concentration decreased in serum obtained at 6 and 12 h after calving in primiparous and multiparous cows; however, while in multiparous cows serum Ca concentrations returned to values similar to those registered before calving, in primiparous animals, values at 6 and 12 h remained lower than in the prepartum sample but increased at 7 days postpartum. Subclinical hypocalcemia (Ca < 2 mmol/l) (Goff, 2008; Reinhardt et al., 2011) in the first hours postpartum was observed in 9 (66%) of the primiparous and 11 (71%) of multiparous cows. There were no cases of parturient paresis.

The prepartum serum P concentrations were higher in primiparous than in multiparous cows, these values decreased at 6 h and remained lower at 12 h and 7 days postpartum in primiparous cows; in multiparous cows, there was no difference between any of the samples (Figure 1). Serum Mg concentration remained unchanged at 6 h but increased at 12 h and 7 days postpartum compared to prepartum concentration in both groups (Figure 1).

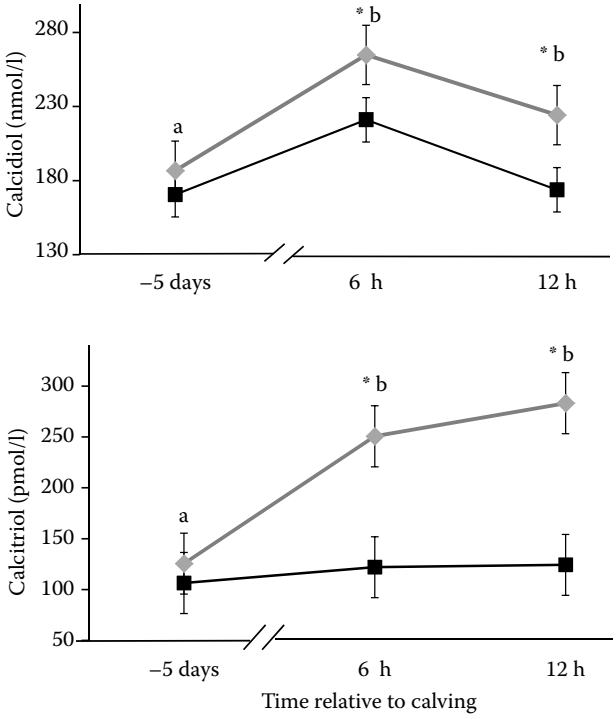

Figure 2. Serum calcidiol and calcitriol in multiparous (◆; n = 16) and primiparous (■; n = 14) dairy cows before and after calving (mean ± SD)

means with different letters differ significantly (P < 0.05), *significant difference (P < 0.05) between multiparous and primiparous cows at the same sampling time

Table 2. Colostrum production, calcium colostrum concentration, and total colostrum calcium in the first postpartum milking in primiparous (n = 14) and multiparous (n = 16) dairy cows

	Primiparous	Multiparous
Colostrum (l)	5.0 ± 0.36[a]	7.13 ± 0.81[b]
Calcium (g/l)	2.05 ± 0.13[b]	1.62 ± 0.15[a]
Total calcium (g)	10.24 ± 1.05	11.97 ± 2.06

[a,b]means within a row with different superscripts differ (P < 0.05)

In multiparous cows, calcidiol concentrations were higher in all postpartum samples than those recorded for the sample collected before calving; in contrast, serum calcidiol concentration did not differ between any samples taken from primiparous cows (Figure 2). Concentrations of this analyte were lower for primiparous than those for multiparous animals in both postpartum samples. Serum calcitriol concentration was similar in both groups 5 days before calving. However, in multiparous cows, calcitriol concentrations at 6 and 12 h postpartum were higher than the prepartum value, in primiparous cows concentrations of calcitriol remained without changes during all the sampling period (Figure 2).

Colostrum production (Table 2) was higher in multiparous than in primiparous cows in the first postpartum milking. In contrast, Ca concentration in colostrum was higher in primiparous compared with multiparous cows. The amount of Ca secreted in the first postpartum milking was similar between primiparous and multiparous cows (Table 2). Serum Ca concentration at 6 and 12 h postpartum had a significant positive correlation with the amount of Ca contained in colostrum (Table 3).

Table 3. Correlation between total Ca (g) secreted in colostrum of the first milking and Ca serum concentration at 5–2 days prepartum, 6 h, 12 h, and 7 days postpartum in dairy cows

	Serum Ca (mmol/l)			
	prepartum		postpartum	
	5–2 days	6 h	12 h	7 days
Primiparous (n = 14)	–0.11	0.26*	0.24**	–0.23*
Multiparous (n = 16)	–0.13	0.18	0.31**	–0.11

*P < 0.10, **P < 0.01

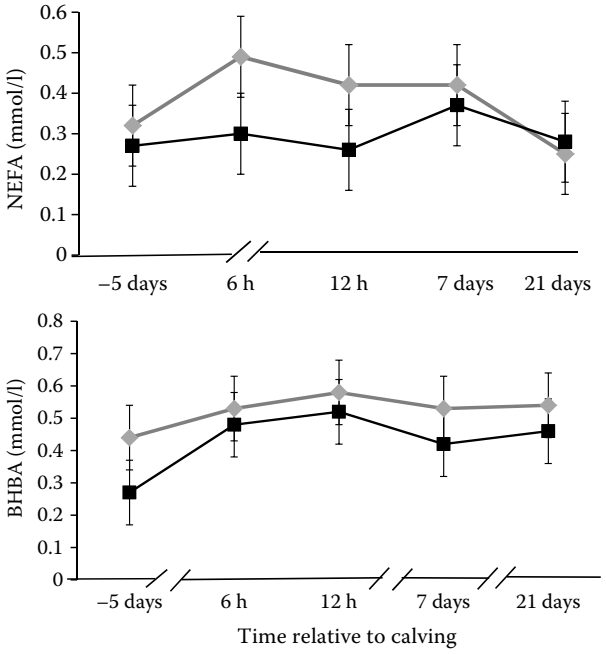

Figure 3. Serum non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHBA) in multiparous (◆; n = 16) and primiparous (■; n = 14) dairy cows before and after calving (mean ± SD)

Serum NEFA did not differ between groups or among samples (Figure 3). Concentration of serum BHBA increased significantly at 6 h postpartum with respect to the prepartum measurement and remained high during the following sampling periods in cows of both groups (Figure 3).

DISCUSSION

In our study, percentage of subclinical hypocalcemia in both groups of cows was higher during the first 24 h postpartum than that reported by Goff (2008), 66 vs. 25% in primiparous and 71 vs. 50% in multiparous cows, probably due to higher concentration of Ca and low concentration of Mg in the prepartum diet. The high incidence of postpartum subclinical hypocalcemia, especially in primiparous cows in our study could be also explained by higher serum concentration of Ca and P than in multiparous cows before calving. Kichura et al. (1982) and Barton et al. (1987) mention that high Ca and P in prepartum diet increase the incidence of hypocalcemia due to inhibition of synthesis of calcitriol; another factor like low Mg and high K and sodium in prepartum diet reduces the efficacy of PTH action (Goff, 2008). The absence of cases of parturient paresis in this work in multiparous cows might be explained by the administration of 500 ml of Ca borogluconate (25%) (28.5 g of Ca) at 6 h postpartum. When a Ca solution is administered intravenously, a rapid increase of Ca in serum is observed but the physiological mechanisms that control plasma calcium concentration regulate concentrations of this ion by elimination throughout kidneys, so by 4 h after injection serum Ca returns to value registered before the application of the Ca solution (Goff, 1999). These increments of blood Ca inhibit PTH secretion and synthesis of calcitriol.

Mg and P play an important role in the pathophysiology of hypocalcemia. It has been observed that PTH secretion and the sensitivity of its receptors decrease when serum Mg is below 0.65 mmol/l (Van de Braak et al., 1986). Serum Mg values were between 0.7 and 1.05 mmol/l in this study, perhaps allowing a better affinity of PTH receptors to the ligand and an adequate physiological response to hypocalcemia. When P content in prepartum diet is relatively high, frequency of hypocalcemia increases (Lean et al., 2006), perhaps because the phosphate ion inhibits activity of 1α-hydroxylase and renal production of calcitriol. This effect occurs when serum P concentration is higher than 2 mmol/l (Kichura et al., 1982; Lean et al., 2006) and such a concentration of P is maintained when P content in the prepartum diet is between 0.21 and 0.45% of DM. However, the diet used in our work contained 0.37% of P and concentrations of serum P were above 2 mmol/l in 63% of all cows, mostly primiparous, before calving, thus recommendations about P concentration in diet perhaps need to be revised, at least for primiparous cows. The decrease in serum P concentration registered postpartum in this work is due probably to the action of PTH on the renal tubules where reabsorption of P declines while Ca increases (Peterson et al., 2005).

Results in this study demonstrate that serum calcidiol concentrations do not change in primiparous cows after calving relative to prepartum concentration; in contrast, calcidiol increases during the first hours postpartum in multiparous animals. To our knowledge, there are no published data regarding the calcidiol concentration in primiparous dairy cows around calving time. In multiparous cows, our results on concentrations or variations of calcidiol relative to calving time differ from those obtained in other studies. While some authors observed that calcidiol concentration does

not differ between cows with or without parturient paresis (Hollis et al., 1981), others found that values of this metabolite before and after calving in healthy (Barlet et al., 1981; Hollis et al., 1981) or paretic (Hollis et al., 1981) cows were similar.

Furthermore, it was published that calcidiol tends to decline after calving in multiparous cows (Bar et al., 1988). Besides, mean concentrations of calcidiol reported by Barlet et al. (1981) and Hollis et al. (1981) were lower in comparison with our data and those from Bar et al. (1988). These differences could be due to the fact that studies of Barlet et al. (1981) and Hollis et al. (1981) were realized in France and Canada, respectively, both during winter, while the study of Bar et al. (1988) was conducted in Israel, where UV radiation is higher than in the countries aforementioned and similar to those registered in La Laguna region, where the present experiment was conducted. Perhaps, higher synthesis rate of vitamin D is due to intensive UV radiation, which induces higher serum calcidiol concentration as it does the supplementation of this vitamin by diet or injection in cows with low concentration of Ca in serum (Yamagishi et al., 2000). The differences in serum calcidiol and calcitriol concentrations could be affected by different laboratory techniques. Even though PTH concentration was not determined in our work, we assume that it was high because the physiological response to hypocalcemia is an increment in PTH release. These results suggest that reduction in serum Ca and/or increase of PTH could positively alter the activity of the 25-hydroxylase enzyme, which increases calcidiol synthesis when vitamin D concentrations are adequate.

The observed increase in calcitriol concentration in multiparous cows is in agreement with results obtained by Horst et al. (1978), who found that cows with parturient paresis had higher concentrations than multiparous cows without that condition. When serum Ca decreases, PTH secretion increases and stimulates the activity of the renal enzyme 1α-hydroxylase, which converts calcidiol into calcitriol. The primiparous cows had sustained concentration of calcitriol along the study and in the samples taken postpartum concentrations of this hormone were lower than in multiparous cows. Other investigators (Horst et al., 1978; Moore et al., 2000) found similar results but cows were normocalcemic, whereas in our study most cows were hypocalcemic. Data from this study corroborate the findings discussed above but only for multiparous cows.

However, our data differ for primiparous cows, because serum Ca concentration decreased in both groups at 6 and 12 h postpartum, but calcitriol concentration in primiparous cows did not change. This allows us to suggest that primiparous cows may not require a fast increase of calcitriol early postpartum, because vitamin D receptors in bone and intestine are more numerous than in multiparous cows (Horst et al., 1990). An alternative mechanism that could inhibit serum calcitriol concentration is that primiparous animals had a higher concentration of Ca and P before parturition than multiparous cows, as was observed in this experiment.

Ca concentration per litre of colostrum was higher in primiparous than in multiparous cows but total amount of secreted Ca in the first milking in primiparous and multiparous cows was not different. These results are consistent with the data observed by Kume and Tanabe (1993). The effect of Ca secreted by the postpartum mammary gland has been discussed in relation to the pathophysiology of hypocalcemia (Kume and Tanabe, 1993; Goff et al., 2002). The onset of colostrum synthesis requires large amounts of Ca. Normocalcemia depends on capacity of cows to mobilize Ca at the beginning of lactation. In past research, hypocalcemia was not present around calving in mastectomized cows, indicating that hypocalcemia is caused by colostrum secretion instead of calving itself (Goff et al., 2002). Although colostrum production was higher in multiparous than in primiparous cows, Ca content in colostrum did not differ, thus meeting demands of Ca under the circumstances of our work may not have been an important challenge for cows since we did not observe any cases of parturient paresis, perhaps because of the preventive measures applied at the farm where the study was performed. In rats, the serum Ca concentration regulates the amount of Ca that passes through the mammary gland by the Ca sensitive receptor and the parathormone-related protein (Van Houten et al., 2004), in ruminant there are not similar studies. The positive relationship observed between Ca serum concentration and total Ca secretion in colostrum indicates that hypocalcemia is not dependent on the amount of Ca yielded by colostrum, at least when colostrum volume yielded is not too high as shown in this study.

Concentrations of NEFA and BHBA remained stable during all the sampling and were in the interval of reference values. These data show adequate

adaptation of cows to negative energy balance occurred as Van de Haar et al. (1999) observed under similar feeding conditions.

CONCLUSION

It was found that only multiparous cows responded to a relatively mild hypocalcemia with a postpartum increase in serum calcidiol and calcitriol. Thus, our first conclusion is that under our experimental conditions, there were sufficient substrates in these cows for synthesis of calcidiol and calcitriol. In primiparous cows, prepartum serum concentrations of Ca and P were higher than in multiparous cows, despite this, primiparous cows presented hypocalcemia of the same magnitude as multiparous animals without a response in calcidiol and calcitriol. Based on this, the second conclusion is that high prepartum serum concentration of Ca and P inhibited the postpartum response of calcidiol and calcitriol but hypocalcemia remains moderate by mechanisms that our data may not explain. Total Ca in colostrum was similar in primiparous and multiparous cows and there was a positive association between serum and colostrum content of Ca; therefore, our third conclusion is that total Ca yield in colostrum is not the main factor of the severity of hypocalcemia.

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