Being a Mom is Hard: Calcium Demands of Early Lactation Dairy Cows

Jessica McArt

Cornell University, Ithaca, NY
Email: jmcart@cornell.edu

■ Take Home Messages

- Hypocalcemia is a common disorder immediately after calving.
- Subclinical hypocalcemia (cows with low blood calcium without clinical signs) is much more common than clinical hypocalcemia (milk fever).
- A drop in blood calcium is normal the day after calving, but blood calcium concentrations should return to normal levels within four days in milk.
- There are no good on-farm tests to determine blood calcium concentration, so herd-level prevention is key.
- Good transition cow management and nutrition is imperative to reducing the impact of subclinical hypocalcemia.
- Postpartum calcium supplementation can be used in target populations, such as older cows, cows with calving difficulties and lame cows, to optimize your return on investment.

■ Introduction

One of the many challenges facing dairy cows around the time of calving is the maintenance of blood calcium concentrations. The daily maintenance requirement of calcium (the amount necessary for normal bodily functions) for a non-lactating cow is approximately 21 g. A single milking of colostrum takes an additional 23 g of calcium, and when a cow is producing 45 kg of milk per day, a yield easily attained within one week of calving, a cow requires an additional 56 g of calcium per day. Thus, her calcium requirement triples in less than one week! This sudden increase in calcium demand occurs in combination with a 30% decrease in feed intake near calving, which restricts this essential macromineral during a critical period.

Postpartum hypocalcemia occurs because of this massive calcium requirement needed to initiate and sustain lactation. To maintain calcium concentrations at a level required for life (e.g., thermoregulation, muscle contraction) while transferring a large quantity to colostrum, cows increase secretion of parathyroid hormone, which increases release of calcium from bone, decreases calcium excretion by the kidney, and indirectly increases intestinal absorption of calcium (Figure 1). Hypocalcemia results when serum calcium concentration falls faster than homeostatic mechanisms can adapt to the demands of lactation.

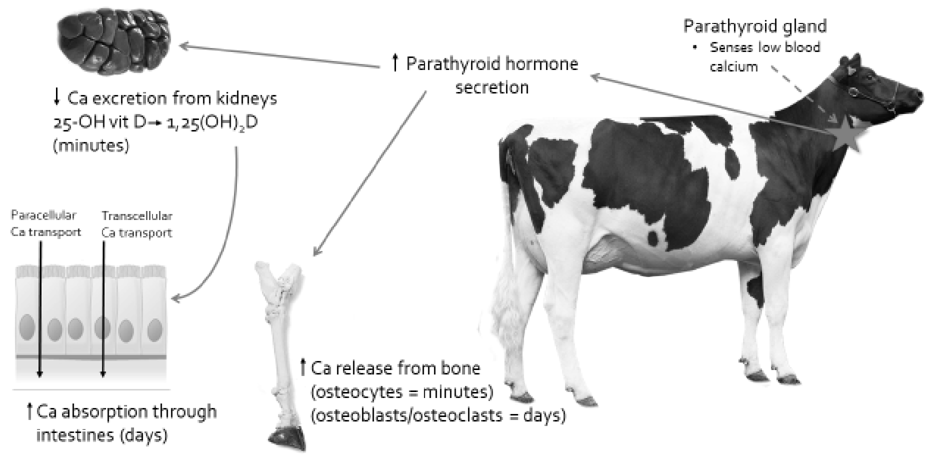

Figure 1. Schematic diagram showing the homeostatic response of a cow to low blood calcium concentration. These mechanisms act in parallel to increase blood calcium to a normal concentration. J. McArt, 2018.

Clinical hypocalcemia (milk fever) affects approximately 2 to 5% of periparturient dairy cattle (Goff, 2008). This disease results in weakness that can progress to recumbency and death and is a widely accepted risk factor for subsequent displaced abomasum, ketosis, metritis, retained placenta, mastitis, culling, and decreased milk production (Goff, 1997; Goff, 2008; Chapinal et al., 2012). Traditionally, subclinical hypocalcemia, a mild form of milk fever in which a cow has low blood calcium but does not show clinical signs, has been defined as a serum calcium concentration <2.0 mmol/l. Reinhardt and colleagues (2011) used this cut-point in samples collected within 48 hours of parturition as part of the 2007 National Animal Health Monitoring System and found that subclinical hypocalcemia is very common in the U.S., affecting up to 50% of postpartum multiparous cows. Recent evidence suggests subclinical hypocalcemia is also a risk factor for future adverse health events, lower milk production, and decreased reproductive performance (Chapinal et al., 2012; Martinez et al., 2012). Surprisingly, little mathematical effort has been placed in the estimation of the economic impact of hypocalcemia, but loose calculations in lay journals by Charles Guard

(Cornell University) and Garrett Oetzel (University of Wisconsin) estimate its cost between $125 to $300 per case.

▪ Diagnostics

The majority of calcium in the blood is in a free or ionized form (50-60%), which is recognized to be the biologically active form responsible for calcium homeostasis. Approximately 30% is bound to proteins, primarily albumin, with another 10% in a complexed form bound with anions (e.g., phosphate, bicarbonate, sulfate, citrate, and lactate). Although ionized calcium makes up most of the blood calcium pool, measurement of the ionized form is expensive and requires special handling of samples; thus, most research has been conducted using total calcium measurements. Although some studies show that total calcium is reasonably associated with ionized calcium concentrations in bovine blood, this relationship changes near calving. Work from Leno et al. (2017) suggests that because of the variation between ionized calcium and total calcium in the few days immediately following parturition, these two measurements of calcium status cannot be used interchangeably; this idea requires further investigation to accurately equate cut-point concentrations for these measurements.

Total calcium is more stable than ionized calcium and is currently the easiest and recommended form to analyze. Blood should be collected into lithium heparin (green top) or preferably non-anticoagulant (red top) tubes; collection into EDTA (purple top), citrate, or sodium fluoride tubes may reduce total calcium concentration to an unmeasurable level due to the calcium binding agents found in these tubes. Whole blood can be stored in a green or red top tube for up to seven days at 4°C with minimal changes in total calcium measurements (J. McArt, personal communication). For best results, however, plasma or serum should be separated as soon as possible. Until recently, the only well-validated way to measure total calcium was via benchtop analyzer. Costs per sample range from US$5 to US$15 at accredited veterinary diagnostic laboratories and many veterinary clinics. This high cost, in addition to the slow turnaround time, makes this method impractical for individual cow monitoring; however, herd-level monitoring, while expensive, is realistic.

Ionized calcium is more problematic to measure because of sample collection and handling difficulties. Exposure of a blood sample to air changes the pH and thus the amount of ionized calcium in the sample; stability over time is questionable, and the sample must be processed as soon as possible. Samples can be submitted to veterinary diagnostic labs or veterinary clinics, but results are often not accurate due to the aforementioned handling difficulties and the time it takes for a sample to arrive at the lab or clinic. Machines targeted for on-farm use (e.g. i-STAT, VetStat, Stat Profile Prime) cost approximately US$5,000 to US$15,000 in addition to per sample costs;

the i-STAT is the only machine with any validation using bovine blood. At US$15 to US$20 per sample, ionized calcium is not currently a cost-effective method of individual animal or herd-level hypocalcemia monitoring on farms, in veterinary clinics, or by diagnostic laboratories.

A German research group, well known for their investigation of on-farm methods of disease measurement (remember the Precision Xtra meter for diagnosis of ketosis?), recently took the historical clinical impression of “cold ears” and applied it to the diagnosis of subclinical hypocalcemia using an infrared thermometer to determine the skin temperature of ears in fresh cows. Unfortunately, although clinically hypocalcemic cows had lower ear temperatures than cows with subclinical hypocalcemia, the ambient temperature confounded the results too much to detect subclinical hypocalcemia via ear temperature alone, making this a non-reliable method of subclinical hypocalcemia diagnosis. Thus, cold ears do not necessarily mean low calcium!

■ Epidemiology

Blood calcium concentrations have been well characterized to reach a nadir (lowest point) between 24 and 48 hours postpartum in dairy cows (Figure 2). However, few epidemiological studies have been conducted to determine the cut-point concentration at which a cow should be classified as hypocalcemic, and even the guidelines mentioned above are a bit arbitrary. In addition, the ideal time postpartum at which to classify a cow as hypocalcemic is just starting to be evaluated.

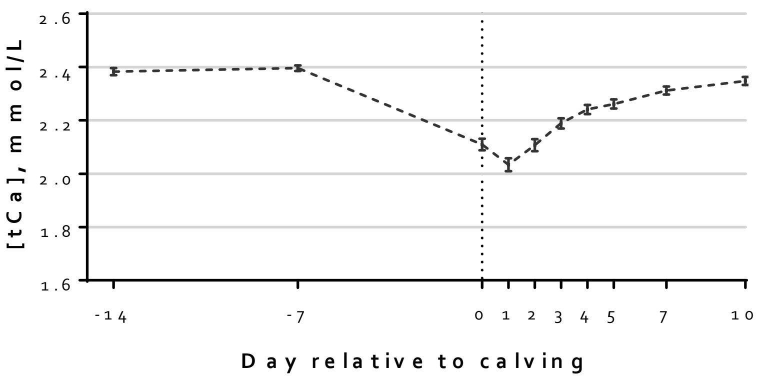

Figure 2. Serum total calcium concentration in 400 Holstein cows from two farms in New York State from 14 days before calving through 10 days postpartum. Data from J. McArt, personal communication.

Interestingly, recent work by Caixeta et al. (2017) shows that cows with total calcium concentrations ≤2.15 mmol/l at one, two, and three days in milk (DIM), which they termed “chronic subclinical hypocalcemia”, had a 70% decreased odds of pregnancy to first service compared to normocalcemic cows. Thus, perhaps it is the persistence of hypocalcemia, not the absolute concentration, which is detrimental to the immediate postpartum cow. The study by Caixeta and colleagues, which involved 97 Holstein cows, also showed that this persistent hypocalcemia occurs in all parity animals, with a higher incidence amongst multiparous cows (20%, 32%, and 46% of parity 1, 2, and ≥3 cows, respectively). This idea is supported by recent results by Neves and colleagues (2018a,b) which show that clinically normal cows with low calcium concentrations at calving and one DIM are less likely to develop early lactation diseases and actually produce more milk in early lactation than cows with normal blood calcium concentrations. Taken together, these studies suggest that we may need to change the focus of our preventative strategies from cows with low calcium concentrations immediately postpartum to those with persistent hypocalcemia. Multiple groups are currently focused on finding answers to these questions.

We do not yet have great data on herd-level hypocalcemia prevalence and its association with adverse health events and production parameters. Chapinal and colleagues (2011, 2012) found adverse health and production effects for cows with calcium <2.1 mmol/l within the first week of calving; however, an acceptable herd-level prevalence has not yet been determined. In general, routine monitoring is never a bad idea given that the economic resources and labour are available to do so. Statistically speaking, a prevalence sample should include blood samples collected from at least 20 cows, and my current recommendation is to collect those samples between 48 and 96 hours postpartum. As mentioned above, these timing recommendations and cut-point thresholds for diagnosis may change. Currently, based on our work (Neves et al., 2018b), I recommend testing cows at four DIM with a cut-point of 2.2 mmol/l to diagnose subclinical hypocalcemia. More knowledge in this area is necessary, and research is currently under way to better describe subclinical hypocalcemia monitoring and response on a herd level.

■ Prevention

Because hypocalcemia increases the risk that a cow will experience adverse health events during her lactation, prepartum management aimed at preventing hypocalcemia also represents a sizable opportunity for preventing other post-partum diseases. The nutritional strategy of reducing the dietary cation-anion difference (DCAD) is the mainstay of hypocalcemia prevention, although vitamin D supplementation or provision of a calcium-deficient diet are also used (Goff, 2008). Cows fed low DCAD rations develop mild acidosis which increases tissue sensitivity to parathyroid hormone, allowing faster mobilization of calcium when demand increases. Some evidence suggests that feeding a low DCAD ration can reduce the incidence of periparturient hypocalcemia from 50% to 30% (Oetzel, 2004). Current recommendations are to feed a DCAD diet of approximately -10 to -15 mEq/100 g of dry matter for three weeks before expected calving (Charbonnear et al., 2006). Leno et al. (2017) showed that plasma calcium concentrations increased linearly in the postpartum period for cows fed a prepartum diet without anion supplementation, partial anion supplementation, or full anion supplementation at +18.3, +5.9, and -7.4 mEq/100g of dry matter, respectively, for four weeks before parturition.

The close-up diet can be adjusted for the DCAD level using either commercial products or through the nutritionist's formulation of feed ingredients. While some commercial products and formulations have improved palatability, feeding a low DCAD may decrease feed intake, so routine monitoring of dry matter intake is important. Proper diet mixing and feeding strategies are also imperative! To ensure the diet is being fed appropriately, monitor urine pH in close-up dry cows. Measure at least 12 to 15 cows each week via midstream urine samples. Meters for pH measurement (e.g., LAQUAtwin, US$175) are quite accurate (and handy for measuring other things on dairies), but litmus paper will give you a reasonable reading for much less money. If you use these pH strips for measuring urine pH, make sure to purchase those with a smaller pH range (e.g. 5.5 to 8.0) so you can really focus on the target range of 5.5 to 6.0 (normal urine pH ~ 8.0). While some cows' urine will be < 5.5 or > 8.0, it is only important to note that a cow is above or below this range; the exact pH measurement is not necessary. Some dairies will report feeding a low DCAD with resulting normal urine pH values. In this case, cows are likely not consuming their expected dry matter, the TMR is not mixed properly, or there has been improper evaluation and adjustment in the ration for free-choice minerals or other forage content. If there is a large variation in urine pH between cows, this indicates an unequal consumption of the ration within the feeding group. This may be the result of social factors, overcrowding or feed sorting due to poor mixing. Variation in urine pH distribution between weeks may indicate inconsistency in ration mixing or changes in feed ingredients that change the DCAD. Use the urine pH monitoring information to improve feeding strategies!

▪ Postpartum Intervention

Given the technological constraints of accurately measuring calcium and the negative consequences of hypocalcemia on dairy cattle health and farm economics, many cows are commonly supplemented with calcium immediately after calving, which can become an expensive and time-consuming task. Common on-farm interventions include subcutaneous or intravenous administration of calcium salts, oral administration of calcium pastes or boluses, or oral drenching with calcium propionate. A lack of progression to clinical symptoms of milk fever is often used to measure the benefits of these interventions, which overlooks the importance of monitoring and treating subclinical hypocalcemia.

The standby therapy for clinical hypocalcemia is intravenous administration of 500 ml of 23% calcium gluconate, which can also be given subcutaneously as a treatment or preventative for subclinical hypocalcemia. Although cows with milk fever need an immediate source of calcium, caution should be used given the potential “rebound effect” found after intravenous administration of calcium, when blood calcium concentrations decrease approximately four hours after administration (Blanc et al., 2014). Cows with clinical hypocalcemia thus benefit from an additional sustained calcium source after intravenous calcium administration. My recommended treatment for cows with milk fever is administration of 500 ml of 23% calcium borogluconate followed by administration of oral calcium 4–8 hours later with a second administration of oral calcium 12–24 hours later.

For prevention of subclinical hypocalcemia, the main products available are subcutaneous and oral calcium. Intravenous calcium should not be administered to standing cows because it is an unnecessarily large amount of calcium for these cows and likely does more harm than good. Although subcutaneous calcium shows a similar but much less severe “rebound effect” than intravenous calcium, this has not been found to be clinically relevant (Figure 3; Domino et al., 2017). Oral calcium supplements usually contain differing combinations of calcium chloride, calcium sulfate, calcium propionate, and calcium carbonate. Calcium chloride is highly bioavailable and acidifying (supporting mobilization of the cow’s own calcium stores) but is irritating to oral mucous membranes. Calcium propionate is absorbed more slowly than calcium chloride, but has equivalent efficacy and longer duration of action, whereas calcium carbonate is ineffective as an immediate calcium source because of to its poor bioavailability and alkalinizing effect. Several manufacturers have introduced oral calcium boluses containing rapidly- and slowly-absorbed calcium salts. Depending on the product, label instruction require administration of one to three boluses at calving, with some products requiring a second bolus administration 12 hours later.

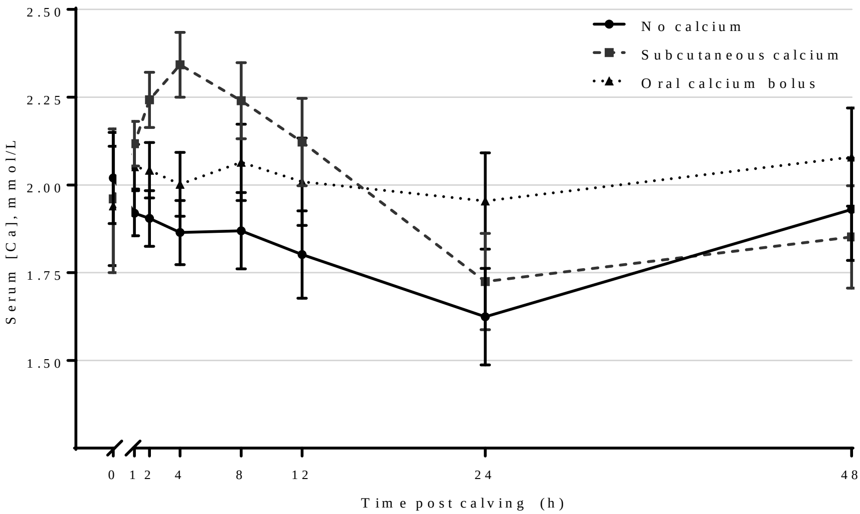

Figure 3. Serum total calcium concentration in three groups of multiparous Holstein cows followed for 48 hours after calving (n = 10 per group). The three groups included: no postpartum calcium supplementation (solid line), 500 ml of 23% calcium borogluconate administered subcutaneously at 0 hours (dashed line), and an oral calcium bolus containing 43 g of calcium administered at zero hours with a second bolus administered at 12 hours (dotted line). Adapted from Domino et al., 2017.

Oetzel and Miller (2012) showed that use of oral calcium boluses decreased adverse health events for lame cows and increased milk production in high-producing multiparous cows, but they could not recommend them as a blanket treatment. Miltenburg et al. (2016) also showed that although subcutaneous calcium administration temporarily increased blood calcium concentrations, it did not affect health or milk production. Given these results and others, it is likely unnecessary to use a blanket prevention strategy for subclinical hypocalcemia if prepartum nutrition and cow comfort management are appropriate. However, these studies also show that older cows, cows with difficult calvings, and lame cows do benefit from calcium supplementation because it reduces disease and improves production.

▪ Conclusions

Although clinical hypocalcemia is becoming a rare occurrence on modern dairy farms employing good nutritional and cow comfort management strategies, subclinical hypocalcemia is an often under-diagnosed problem at both the individual animal and herd levels. Current research is underway to better define the epidemiology of hypocalcemia on today's commercial herds with high producing cows. Testing and monitoring options remain expensive although studies to improve on-farm, economically-viable testing methods are underway. Prevention of hypocalcemia through peripartum nutritional management is key.

Conflict of Interest Statement

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