TECHNOTE: The Transition Cow: Relation of Metabolic Disease and the Immune System
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The transition period, three weeks before and after calving is the most challenging time in the lactation of a dairy cow, due to the immune system being compromised. Most of the metabolic diseases of dairy cows, retained placenta, milk fever, ketosis, and displaced abomasum occur within the first two weeks of lactation. In addition to metabolic diseases, the majority of infectious diseases experienced by the dairy cow, especially metritis and mastitis, but also Johne's disease and Salmonellosis, become clinically apparent during the same time frame.

Neutrophil and lymphocyte function is diminished in the periparturient period of the dairy cow. The onset of milk production imposes tremendous challenges to the homeostatic mechanisms, turning the cow to a negative energy, protein, and/or mineral balance, which may be partially responsible for the immunosuppression observed during this time. Also, around two days before calving progesterone level drops and estrogen level rises. Estrogen is one of the players in immunosuppression during calving. (Goff, 2006).

Associations between metabolic diseases
Several epidemiological studies have demonstrated that there is an association between the development of metabolic disease and subsequent development of mastitis. In a study of NY dairies (2,190 cows) there was a strong association between parturient hypocalcemia or milk fever and mastitis. The odds ratio suggested that a milk fever cow was 8.1 times more likely to develop mastitis than a cow that had not had milk fever. 25% of coliform mastitis cases occur in the first 2 weeks of lactation. Calcium is necessary for proper contraction of muscle. The contraction rate and strength of the smooth muscle of the intestinal tract is directly proportional to blood calcium concentration. The teat sphincter consists of smooth muscle which must contract to close the teat end. If low blood calcium reduces teat sphincter contraction the teat canal may remain open inviting environmental pathogens to enter the mammary gland, and many cows remain subclinically hypocalcemic for the first week of lactation (Goff et al., 1999).
Intracellular calcium signaling is a key early feature in immune cell activation. The increased demand for calcium in periparturient cows may adversely affect intracellular calcium stores of immune cells. A Holstein cow has about 11g of extracellular Ca and 3.5g of blood serum Ca. After calving she will need about 20-30g of Ca to produce milk. This will cause a reduction in intracellular calcium, contributing to the immune suppression seen in these animals.

Hypocalcemia and Metritis
Surveys in the United States indicate that 25% of primiparous and 45% of the multiparous cows will develop subclinical hypocalcemia (SCH) in the first week of lactation. Cows with less than adequate serum Ca concentrations have compromised health because of increased risk of developing uterine prolapse, retained placenta, metritis, displaced abomasum, and ketosis. Therefore, prevention of hypocalcemia should go beyond minimizing milk fever, but also reduce the prevalence of cows that develop SCH. SCH is defined as total Calcium levels in the blood below 8.59 mg/dl during day one, two and three postpartum.

Martinez et al., 2012, documented that cows with SCH in the first three days postpartum had three-fold greater risk of developing metritis, compared with cows with normal blood Ca after calving. These cows with SCH also had increased incidence of endometritis, a disease that is less recognized by producers and characterized by presence of pus in the uterus after three weeks postpartum. In fact, cows with SCH had immune cells with impaired function, which is thought to explain some of the inability to eliminate the bacterial contamination with the onset of parturition. Not only they had increased risk of uterine diseases, but they also had compromised reproductive performance. The interval from calving to pregnancy extended from 109 days in normocalcemic to 124 days in cows with SCH. They had two groups of cows: a high risk, which were cows that had experienced dystocia, retained placenta, twins or stillbirth; and a low risk group, which were cows that calved normally. The low risk cows with SCH had more metritis (40.7%), compared with
normal cemic cows (14.3% had metritis). The high risk cows with SCH had more metritis (77.8%) compared with normal cemic cows (20%). Also cows with SCH had reduced neutrophil function and higher NEFA and BHB.

Ketosis
In early lactation, the amount of energy required for maintenance of body tissues and milk production exceeds the amount of energy the cow can obtain from her diet, because dry matter intake is still low. On average, dry matter intake decreases by 20-30% one or two days before calving, and does not recover until one to two days after calving (Bertics et al., 1992). As a result, the cow must utilize body fat as a source of energy. Every good cow will utilize body reserves in early lactation to help her make milk. However, there is a limit to the amount of fatty acid that can be handled and used for energy by the liver (and to some extent the other tissues of the body). When this limit is reached, the fats are no longer burned for energy but begin to accumulate within the liver cells as triglyceride. Some of the fatty acids are converted to ketones. The appearance of these ketones in the blood, milk, and urine is diagnostic of ketosis. As fat accumulates in the liver it reduces liver function - and a major function of the liver in the dairy cow is to produce glucose.

Cows with Ketosis produce less Interferon
In a Swedish study, ketosis increased the risk of mastitis two-fold (Oltenacu and Ekesbo, 1994). A second and larger study (18,110 Swedish Red and White cows in 924 herds and 14,940 Swedish Friesian cows in 772 herds) found that the risk of mastitis was increased in cows that had suffered a retained placenta (Emanuelson et al., 1998). Interestingly, liver biopsies showed that liver triglycerides were increased three-fold by the day of calving. Triglyceride buildup in the liver happens much earlier than previously assumed.
Even more interesting; when cows were fitted with rumen fistulas and dry matter intake was not allowed to drop around the time of calving by forcing feed into the rumen, liver lipids and triglycerides increased only a small amount. Energy intake must not be compromised during the days around calving. Any factor restricting feed intake before calving, such as overcrowding, pen moves, heat stress, lack of cow comfort or after calving, such as dystocia, milk fever or retained placenta increases fat accumulation in the liver, affecting the energy deficit of the cow and increasing the risk of fatty liver-ketosis.

The fresh cow is also in negative protein balance shortly after calving. Generally this is not perceived to be as big a problem as the negative energy balance of early lactation but the typical cow will lose 37 lbs body protein during the first two weeks of lactation, causing these cows to be short of essential amino acids, which are needed to produce white blood cells to fight infections. The lifespan of neutrophils is about 12 hours. Much of this body protein is being used to support the amino acid and glucose requirements of milk production.

Cow comfort and social behavior of transition cows are as important as diet formulation. The picture below shows the difference in milk production and mortality rate of cows based on days the cows spent on closeup pen.

Cows that spent over 21 days in closeup pen made more milk and had lower mortality rate

Granulocyte-Colony Stimulating Factor (G-CSF) and Immune Function Around Calving

Granulocyte colony-stimulating factor is a glycoprotein cytokine that stimulates the bone marrow to produce stem cells and granulocytes and release granulocytes into the bloodstream to form Polimorphonuclear Neutrophils (PMN), making the immune system stronger to combat infections. A recombinant form of human granulocyte colony-stimulating factor is used for certain cancer patients to accelerate recovery from neutropenia after chemotherapy (Lyman et al., 2013).

In an attempt to improve PMN functional capacity during the periparturient period, Kimura et al, 2014 injected cows with recombinant bovine granulocyte colony stimulating factor covalently bound to polyethylene glycol (PEG rbG-CSF) twice subcutaneously, about six days before calving and within 24 hours after calving. 21 cows in their second pregnancy were enrolled in this study and divided into two groups: PEG rbG-CSF treated (n = 11) and saline-treated controls (n = 10).

The PMN numbers quickly and dramatically increased after PEG rbG-CSF administration and remained elevated through the end of the experiment (13 days after calving). The greatest single effect of PEG rbG-CSF administration was a dramatic increase in circulating numbers of PMN. The increased numbers of PMN ready
to move to a site of infection early in the course of an infection may improve the ability of the cow to ward off clinical disease in the periparturient period.

![Graph showing effect of CFS on neutrophil population after calving]

**Effect of CFS on neutrophil population after calving**

**References**


