IMPORTANCE OF ENERGY BALANCE IN TRANSITION COWS TO EFFICIENCY OF DAIRY PRODUCTION AND DISEASE INCIDENCE

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The periparturient or transition period (3 weeks before to 3 weeks after calving) is critically important in determining the health status and efficiency of milk production of a dairy herd. The incidence of infectious and metabolic diseases, including mastitis, metritis, hepatic lipidosis, and ketosis, is highest during this time (Goff and Horst, 1997). These diseases not only negatively impact milk productivity and production costs, but can have long-term detrimental effects on reproductive efficiency (Cook, et al., 2001, Jorritsma, et al., 2000, Loeffler, et al., 1999). It is essential that we identify the factors predisposing dairy cows to these infectious and metabolic diseases during the transition period, so that we can take appropriate steps to prevent and rectify them.

Recently, attention has been directed toward transition dairy cow nutrition and metabolism, particularly on the state of negative energy balance that ensues during this period. Periparturient dairy cows are under substantial energy and nutritional stress to meet the demands of the developing fetus and subsequent milk production (Overton and Waldron, 2004). These factors, coupled with the natural decline in dry matter intake that occurs just before calving, sets up a condition whereby energy intake is insufficient, resulting in a state of negative energy balance in the parturient cow. In this state, energy is derived from metabolism of adipose tissue deposits, which liberates non-esterified fatty acids (NEFA) (Drackley, 1999, Gerloff, 2000, Goff and Horst, 1997, Grummer, et al., 2004, Overton and Waldron, 2004). Thus, elevated NEFA are a biochemical indicator of negative energy balance.

Although NEFAs are used for energy by most tissues, the liver removes many of them in amounts proportional to their blood concentration. Within the liver, they are oxidized for energy in the Kreb's cycle. However, if NEFA uptake overwhelms the liver's capacity for oxidation, the excess NEFAs are metabolized to ketone bodies, including beta-hydroxybutyrate (BHB), or re-esterified to form triglycerides (TG). Ketones are excreted back into the blood and transported to mammary tissue where they are used for milk fat synthesis. However, dairy cows have a uniquely poor capacity to export triglycerides and excess are stored within hepatocytes, causing hepatic lipidosis(Bruss, 1993, Herdt, 2000a). To some degree, all transition dairy cows are in a state of negative energy balance and have triglyceride accumulation in their livers, particularly in the 48 hours preceding calving and in early lactation (Drackley, et al., 2001, Dyk, 1995, Herdt, 2000a). However, if negative energy balance in the crucial last weeks before calving is excessive, the accumulation of triglycerides and ketones becomes detrimental to the animal's health and productivity.

Diseases associated with negative energy balance

Cows in negative energy balance (based on high NEFA concentrations) are more prone to developing postparturient metabolic and infectious diseases (Cameron, et al., 1998, Dyk, 1995, Gerloff, 2000, Grummer, et al., 2004, Herdt, 2000a). Several studies have shown that improving energy intake in the crucial final weeks before calving can decrease NEFA concentrations and the degree of hepatic triglyceride accumulation (Doepel, et al., 2002, Duffield, et al., 1998a, Duffield, et al., 1998b, Studer, et al., 1993, Vandehaar, et al., 1995).By altering hepatic function, fatty liver usually predisposes cows to ketosis, (Dyk, 1995, Gerloff, 2000, Piepenbrink and Overton, 2003). Clinical ketosis occurs in early lactation and affected cows have decreased appetite, rapid and sudden weight loss, a marked decrease in milk yield, and BHB values > 26 mg/dL. However, it is now recognized that dairy cows also suffer from subclinical ketosis. These cows are diagnosed on the basis of elevated BHB concentrations (> 14 mg/dL)(Duffield, 2000). Indeed, the lactational incidence of subclinical ketosis is much higher (up to 50%) than that of clinical ketosis (2-15%) (Duffield, 2000). Subclinical ketosis is detrimental because affected cows have decreased milk production and an increased risk of infectious and other parturient diseases, including metritis, mastitis, displaced abomasums, and retained placentas (Duffield, 2000).

Periparturient immune suppression has many potential causes related to energy balance. Kimura, Goff, and coworkers (1999a, 1999b) have noted that aspects of the blunted response may be due to declining T-cell populations and decreased neutrophil (PMN) function around calving in cows with intact udders versus those that were mastectomized. The predisposition to infectious disease has also been attributed to ketone-induced decreases in leukocyte chemotactic and bactericidal ability (Suriyasathaporn, et al., 2000).It also appears that ketosis and negative energy balance affect reproductive efficiency. Irregular or delayed cycles, increased calving to conception intervals, decreased fertility rates, cystic ovaries, and decreased follicular size have all been linked to high NEFA or BHB (Cook, et al., 2001, Diskin, et al., 2003, Duffield, 2000, Jorritsma, et al., 2000, Pushpakumara, et al., 2003, Walsh, et al., 2007).

Importance of endometritis to efficiency of dairy production and well-being of dairy cows:

After parturition, bacterial contamination of the uterus is ubiquitous in dairy cattle and infection causes clinical disease in up to 40% of animals within two weeks of calving. Up to 15% of animals have persistent metritis for at least 3 weeks (Sheldon, 2004; LeBlanc, 2002). After that, subclinical endometritis, diagnosed by endometrial cytology, is both highly prevalent and has a profound impact on subsequent reproductive performance (Gilbert et al., 2005). Unfortunately there is little known about prevention of this condition. Our study demonstrated that

approximately 53 % of dairy cows in five commercial dairy herds in central New York had cytologic evidence of endometrial inflammation between 40 and 60 days postpartum – immediately preceding the period during which insemination would be scheduled to commence. Other workers have found a similar prevalence of endometritis in dairy cows elsewhere in North America; albeit in a small number of dairy herds (Hammon et al., 2001; Kasimanickam et al., 2004), n=1 and n=2, respectively. In our study, we found herd prevalence of endometritis ranging from 37 to 74 % (n=5). Cows with endometritis had a lower overall pregnancy rate, demonstrated by Kaplan-Meier survival analysis ($P < 0.0001$; see **Fig 3** in Preliminary data). Median days open was 206 for cows with endometritis and 118 for cows free of the condition. Also, significantly fewer cows with endometritis (63%)were confirmed pregnant by 300 DIM compared to cows without endometritis (89%) ($P < 0.003$). Pregnancy to ûrst service percentage was lower (11 versus 36%; $P = 0.001$) for cows with and without endometritis, and these cows required more services before 50% became pregnant (3 versus 2; $P = 0.006$).
Even though few herds are represented in this data, it is clear that there is a marked difference between herds in the percent of cows that have endometritis. The risk factors that lead to this heterogeneity remain unknown at this point. Even the herds with the fewest cases of endometritis stand to lose significantly in terms of reproductive efficiency. Using the difference in median calving to conception intervals between those cows with and those without endometritis and conservatively valuing one extra day open between $1.50 and $2.50 (Meadows et al., 2005, Plaizier et al., 1997) this equates to approximately $175 per cow per lactation. On a 1000 cow dairy this could be in excess of $175,000 per year in lost revenue. Further the well-being of dairy cows is threatened by the significant difference in cows pregnant by 300 DIM due to failure to promise the start of a new lactation.
Although bacterial infection of the postpartum uterus is very common, most authors report few infections persisting beyond four weeks postpartum(Hammon et al., 2001, 2006; Gilbert et al., 2004b; Kasimanickam et al., 2004; Sheldon et al., 2006). Interestingly, our recent findings have shown a relationship between recruitment of neutrophils to the uterus on the day of calving and subsequent endometrial infection and persistent inflammation. Cows recruiting the most neutrophils on the day of calving had the least risk of subsequent disease (Gilbert et al., 2007). This demonstrates that there is an important relationship between the physiological role of neutrophils in normal periparturient uterine physiology, and their role in postpartum uterine disease. Thus, the relationship between bacterial contamination or infection of the uterus and persistent inflammation remains to be clarified.
Although postpartum infection and persistent subclinical endometritis are common in dairy cows, they are not universal. Some cows rid themselves of uterine bacterial contamination and inflammatory cells promptly. It is not clear what differentiates affected from unaffected cows and herds with high prevalence from herds with low prevalence. It is likely that heretofore undetermined relationships between periparturient energy balance and immune response explain a significant portion of this difference.

Likely relationship between energy balance, liver metabolism, immunity, and endometritis:
During the past several years, increasing attention has focused on the potential relationship of metabolic status during the transition period with subsequent reproductive performance (review, Jorritsma et al., 2003, Walsh et al., 2007). Part of this attention has focused on a negative association between liver triglyceride accumulation, negative energy balance and various indices of reproductive function. Although it is unclear whether the relationship between increased liver triglyceride accumulation and impaired reproductive performance is a direct effect of the processes described above (gluconeogenesis and ureagenesis), it is apparent that they are impaired by excessive accumulation of triglycerides.

As an example, Marr, Overton and coworkers (2002) categorized cows as ovulatory or nonovulatory based upon whether or not the first dominant follicle detected during early lactation actually ovulated. They determined that cows categorized as ovulatory not only had lower circulating concentrations of NEFA and BHB and lower liver triglyceride (TG) concentrations compared to nonovulatory cows, but that ovulatory cows accumulated less liver triglyceride in proportion to circulating NEFA. This finding suggests that factors specifically related to liver capacity to dispose of NEFA either through oxidation or export may be important for subsequent reproductive function. Interestingly, Piepenbrink and Overton (2003a) reported that triglyceride accumulation was more highly correlated with circulating BHB than with circulating NEFA, suggesting the importance of factors associated with NEFA disposal, rather than NEFA concentrations, as risk for metabolic disorders such as ketosis.Oelrichs et al. (2004a; 2004b) fed dairy cows 15 g/d of choline in a rumen-protected form from 28 d before expected parturition until 100 days in milk. They determined that choline supplementation decreased circulating concentrations of NEFA and BHB and increased milk yield during early lactation.

In a study conducted by Zerbe and coworkers (2000) they demonstrated that multiparous cows with liver TG content greater than 40mg/g in the post-partum period had decreased neutrophil (PMN) function in cells derived from the peripheral blood with an even greater loss of those from the uterus. This liver metabolism work was recently bolstered by energy balance experiments by Hammon and coworkers (2006) who showed that dry matter intake (DMI) and energy balance, starting in the prepartum period, were related to innate immunity and postpartum uterine health in their university herd. Of 83 cows, those with the lowest 25% of DMI had significantly lower neutrophil (PMN) myeloperoxidase activity compared to those cows with the highest 25% DMI indicating that those cows with lower DMI had less bacterial killing ability. Further, in 53 cows they showed the myeloperoxidase activity was negatively correlated with NEFA concentration one week after calving. This appeared to translate into development of endometritis as cows with that condition had significantly higher NEFA levels 2 weeks prior to parturition and higher BHB levels 1 to 4 weeks after calving as compared to cows with normal uterine health.