Transition Cows - How Fatty Acids Affect Immunity, Production and Health

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Introduction

The transition to lactation remains one of the most challenging and important phases of the production cycle. We continue to gather more insight into the specific mechanisms underlying this transition, but the basic challenge is the cow at this time needs to rapidly shift gears while she's under many forms of stress – metabolic, immunological, and even social. The list of nutritional interventions that have been tested for aiding this transition is lengthy, with wide variation in the evidence supporting product use. The focus of this article is on the bioactivity of fatty acids that can be fed to transition cows, the processes in the cow that may be altered, and the functional impacts of such strategies on the transition cow. As we'll see, fatty acids have a wide variety of impacts that make this an exciting avenue to potentially improve transition cow health and performance.

The Transition Puzzle

Transition cows present something of a paradox. Despite moving into a physiological state where nutrient requirements generally increase by 2 to 5-fold in the course of a week or two, they often show poor feed intake. The cause of this predicament is not fully understood, but we do know that most transition cows experience at least a few days of systemic inflammation after calving, and inflammatory molecules inhibit appetite. Those cows who resolve the inflammatory state quickly are likely to be the ones who show a strong improvement in feed intake in the first week of lactation.

Likewise, calving and the onset of lactation introduce new avenues for microbial invasion, and infectious disease risk is greater during this time than the rest of lactation. Unfortunately, altered immune function at the same time seems to make it hard for cows to combat this increase in disease pressure. Circulating neutrophils (the key rapid-response immune cell type) decline after calving, and there is some evidence of reduced humoral immunity as well (impaired antibody production). Enhancing immune function may be especially important for subsequent fertility, as those cows with a strong uterine immune response in the first 2 weeks after calving generally avoid chronic endometritis and have increased odds of becoming pregnant at first service. Further complicating efforts to help the cow with dietary or pharmaceutical "nudges" is the issue that inflammation is a key component of the immune response. We thus have

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the difficult task of trying to reduce inflammation (thereby, we hope, enhancing appetite) while promoting immune response to better resolve metritis and mastitis. These are not readily compatible goals! Nevertheless, dietary lipids may help us to strike the right balance between these competing objectives.

Fatty Acids- The Original Bioactive Nutrients?

The big shift that is driving much nutrition research today is the understanding of nutrients as signals rather than just fuels and building blocks (Bradford et al., 2016). This shift in thinking arguably started with research into mechanisms by which polyunsaturated fatty acids alter gene expression, which revealed nuclear receptors that bind fatty acids and then interact with DNA. Prior to these discoveries, only drugs and hormones were thought to work through such receptors. Since that time, cell-surface receptors have been discovered that also respond to fatty acids and their downstream metabolites. Therefore, fatty acids not only provide energy and serve as a structural component of cells, but they also have multiple avenues for changing the function of cells and organs.

To add another layer of complexity to this, dietary triglycerides are rapidly cleaved to free fatty acids in the rumen, and microbial biohydrogenation then substantially alters the composition of fatty acids leaving the rumen. Although the majority of dietary fatty acids are completely saturated through this process, there are intermediates that escape the rumen, and composition of these intermediates is influenced by dietary fatty acid profile, microbial populations, and rumen chemistry. Calcium salts of fatty acids are less available for microbial modification in the rumen compared to free oils, but they are not totally inert. In fact, less than 25% of a polyunsaturated fatty acid fed to a cow will be absorbed in that form (Lundy et al., 2004; Harvatine and Allen, 2006), so we have to keep that in mind when supplementing bioactive lipids. Despite this challenge, we have evidence that dietary lipids can alter the physiology of transition cows in important ways. Let’s dig into a few key strategies that have been attempted for aiding the transition to lactation.

Energy Balance

Many cows experience a month or more of negative energy balance postpartum, resulting in body condition loss. Rapid body fat mobilization is a risk factor for metabolic diseases in early lactation, and this weight loss also impairs fertility. Dietary fat sources provide a possible means to increase energy supply for cows in early lactation; however, increasing energy *density* may not increase energy *supply* if feed intake decreases. Intake responses are important to consider, because unsaturated fat sources in particular can substantially decrease intake (Bradford et al., 2008). One recent study with 48 cows explored responses to 2% saturated fatty acids fed during the first 30 days of lactation. Surprisingly, cows offered diets including supplemental fat actually consumed more feed than cows on the control diets (Piantoni et al., 2015). Although dietary fat clearly slowed the loss of body condition in early lactation, it did not improve milk production; in fact, the saturated fatty acid treatment decreased milk yield during peak lactation (after treatments ended) by 8%. Therefore, in spite of nice improvements in early lactation energy intake, subsequent benefits were lacking.

More recent work at Michigan State has explored the impacts of feeding specific fatty acids to fresh cows. Supplementing palmitic acid in the first 24 days of lactation significantly increased milk fat yield compared to no supplemental fat (de Souza and Lock, 2019), similar to effects in mid-lactation cows. However, palmitic acid appeared to have an impact beyond just driving more palmitic acid content in milk; loss of both body condition and body weight was greater in cows on this treatment. A follow-up study then evaluated fresh diets (24 days) supplemented primarily with palmitic acid, but also including 10, 20, or 30% oleic acid. The dose-response to oleic acid was impressive – as its inclusion increased, dry matter intake increased, blood insulin increased, and body weight loss was slowed (de Souza et al., 2018). How can adding small amounts of such a common fatty acid impact transition cow energy balance like this? Follow-up research suggested that oleic acid administration significantly decreased the lipolytic response of bovine adipose tissue and increased insulin sensitivity, which would promote lipid storage rather than release (Laguna et al., 2019).

Conjugated Linoleic Acid

One intriguing approach to manipulating energy balance in early lactation is the dietary supplementation of conjugated linoleic acids (**CLA**). There are several forms of CLA produced within the rumen during the biohydrogenation of polyunsaturated fatty acids. One form, *trans*-10, *cis*-12 CLA, is produced in the rumen primarily when diets with excessive rumen-available unsaturated fatty acids and inadequate fiber substantially change ruminal biohydrogenation. *Trans*-10, *cis*-12 CLA is believed to be largely responsible for the suppression of milk fat synthesis in these scenarios, and it also promotes adipose tissue fat synthesis. Although this is typically avoided by dairy nutritionists, in early lactation, suppressing milk fat secretion could decrease milk energy content and help to partially restore energy balance.

A series of studies conducted in Germany has evaluated responses to feeding a product that serves as a potent source of mixed CLA, including the *trans*-10, *cis*-12 isomer. Unfortunately, most results have been disappointing. Although feeding CLA has consistently decreased milk fat concentration in transition cows as proposed, cows fed this product have simply responded by increasing milk yield (von Soosten et al., 2011) and/or decreasing dry matter intake (Schäfers et al., 2017). The net result in nearly every study has been a neutral effect on energy balance, with no clear evidence of a more rapid end to body weight loss.

Dietary Fat Can Influence Transition Weight Loss

Dietary fatty acids do appear to have the potential to modulate partitioning of energy between the mammary gland and other organs in early lactation, with the most promising responses to date being with oleic acid. Further research into specific mechanisms driving changes in adipose tissue metabolism with oleic acid may open up opportunities to more dramatically change the trajectory of body weight loss in early lactation cows.

Inflammatory Signaling Pathways

Most endocrine signals in the body are protein hormones, but there are also important lipid hormones. Lipid hormones include cholesterol-derived steroids and the broad group known as eicosanoids or oxylipids. Eicosanoids include some relatively familiar signals like prostaglandin $F_{2\alpha}$, but there are dozens of other less-familiar compounds in this class, many with roles that are still emerging (Sordillo, 2018). From a nutritionist's point of view, these endocrine factors are of great interest because eicosanoid concentrations are heavily influenced by the availability of their fatty acid substrates. Eicosanoids are derived from omega-6, omega-3, and sometimes omega-9 unsaturated fatty acids, and to paint with a broad brush, the omega-6 derived eicosanoids promote inflammatory processes, whereas those downstream of omega-3 fatty acids tend to drive resolution of inflammation.

Studies have documented that transition cows experience a shift in the profile of eicosanoids in blood, with more inflammatory lipids generally increased during this period compared to established lactation (Kuhn et al., 2017). Furthermore, transition cows challenged with additional inflammatory insults had a delay in the recovery of anti-inflammatory eicosanoids in the first week after calving (Yuan et al., 2013). Eicosanoids clearly participate in the systemic inflammatory shift after calving, which may be important, given the associations between inflammatory markers, health, and productivity in transition cows (Bradford et al., 2015).

Dietary unsaturated fatty acids serve as substrates for these eicosanoids, and the fatty acids themselves can influence inflammatory tone as well (Oh et al., 2010). Is it possible to alter transition cow inflammation by feeding different sources of fat?

Altering Omega-6:Omega-3 Ratio

Omega-3 fatty acids include alpha-linolenic acid (**ALA**), eicosapentaenoic acid (**EPA**), and docosahexaenoic acid (**DHA**). Omega-6 fatty acids are more abundant in the diet and in the cow, with the primary form being linoleic acid. With diets typically fed to dairy cows, plasma omega-6:omega-3 ratios generally exceed 10:1. Given the impact of biohydrogenation on absorbed fatty acids, is it possible to impact this ratio? A review of dozens of studies shows that feeding unprotected fish or flaxseed oil (common sources of omega-3 fatty acids) have little impact on plasma omega-3 fatty acids, but that feeding products designed to limit ruminal availability of fatty acids can decrease the plasma omega-6:omega-3 ratio by up to 40% (Moallem, 2018). Therefore, although all of these polyunsaturated fatty acids are absorbed in small quantities in ruminants, some feed products can shift the profile of absorbed lipids.

Impacts on Immunity

Lessard et al. (2003) reported that feeding fresh cows whole flaxseed (a source of alpha-linolenic acid) increased serum omega-3 fatty acid concentration, resulting in a marked reduction in the omega-6:omega-3 ratio compared with those fed micronized soybeans or calcium salts of palm oil. Interestingly, on day 5 after calving, the lymphocyte proliferative response (a component of adaptive immunity) of cows fed flaxseed was reduced compared with other groups, suggesting an anti-inflammatory effect was achieved, albeit not necessarily a beneficial one.

Silvestre and colleagues (Silvestre et al., 2011) attempted to promote immune function in the transition period by supplementing omega-6 fatty acids compared to omega-3 fatty acids, supplied in the form of calcium salts of fatty acids. Increasing the ratio of omega-6:omega-3 fatty acids increased the production of hydrogen peroxide and phagocytosis of bacteria by neutrophils (Silvestre et al., 2011), which could be due to increased supply of omega-6 precursors of inflammatory eicosanoids and/or decreased supply of anti-inflammatory omega-3 fatty acids. This treatment also increased plasma concentrations of 2 acute phase proteins (Silvestre et al., 2011), indicating a more inflamed state of the liver during the transition period. The observed effects on neutrophil function and acute phase response would be expected to improve the ability of the immune system to ward off infection, but like the results of Lessard et al. (2003), it's not entirely clear whether this would be a net benefit for a transition cow. The potential benefits of either approach may depend on the incidence of metabolic vs. infectious diseases on a given farm, the metabolic state of the cows in question, and even the diet to which the fatty acid supplement is added.

Impacts on Productivity

Greco and colleagues (2015) used combinations of calcium salt products to offer cows diets with omega-6:omega-3 ratios of 6:1, 5:1, or 4:1 between 14 and 90 days in milk, while holding total unsaturated fat supply relatively constant. In avoiding the first 2 weeks postpartum, this study bypassed potential impacts on the typical transition inflammation window, but the results were insightful nonetheless. Decreasing the omega-6:omega-3 ratio (increasing omega-3 supply) resulted in significantly greater dry matter intake as well as increased yields of all milk components. An intramammary endotoxin challenge at 75 days in milk demonstrated that some systemic inflammatory responses were elevated for the treatments with greater omega-6 content compared to the 4:1 ratio (Greco et al., 2015). Positive productivity responses to increased omega-3 supply are consistent with impacts of supplying other types of anti-inflammatory agents in early lactation (Carpenter et al., 2016; Olagaray et al., 2019).

Altering Inflammatory Status with Dietary Lipids

Considered together, research to date suggests that diets with elevated concentrations of omega-3 fatty acids (protected in part from ruminal biohydrogenation) can be used to mildly decrease inflammatory status of postpartum cows, which may benefit productivity but potentially dampens immune response. Interpretation of most such studies, furthermore, is complicated by differences in not only inflammation, but also in supply of multiple fatty acids that serve as precursors for eicosanoids, including prostaglandins and other reproductive hormones. One study demonstrated that supplementing *either* omega-3 or omega-6 fatty acids during early lactation increased peak progesterone concentrations during the estrus cycle (Dirandeh et al., 2013), indicating that essential fatty acid deficiency may be a separate issue worth considering.

Conclusions

Despite the challenges associated with sneaking bioactive polyunsaturated fatty acids past the rumen, products available today offer opportunities to alter the transition to lactation. Palmitic acid remains the most potent tool available for enhancing milk fat yield, but oleic acid appears to offer an important means to shift some fat to body stores in the critical first month of lactation. Additionally, the omega-3 and omega-6 fatty acids provide subtle but effective tools to nudge inflammatory tone of transition cows, with omega-3 supplements potentially suppressing inflammation to enhance productivity, whereas omega-6 supplements may enhance immune vigilance and could decrease infectious disease incidence. Dairy nutritionists should consider which fatty acid strategies best address the challenges on individual farms.

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