Impact of Nutritional Strategies, Including Feeding Amino Acids, on Health, Performance and Fertility of Dairy Cows

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Take Home Messages

- Nutritional strategies and feeding management during the pre-calving and post-calving periods affect health, productivity and fertility of high-producing dairy cows.
- Management to improve cow comfort and ensure good intake of the ration is pivotal for success.
- Rumen-protected methionine and lysine added to the diet of Holstein cows during the transition period and early lactation improves the survival rate of preimplantation embryos.
- Impacts of the transition program should be evaluated in a holistic way that considers disease occurrence, productivity, and fertility.

Introduction

Strategies to improve the reproductive performance of dairy cows include alteration of nutritional status. In other species, dietary supplementation with specific amino acids (AA) (e.g., arginine, glutamine, leucine, glycine, and methionine) had beneficial effects on embryonic and fetal survival and growth through regulation of key signaling and metabolic pathways (Del Curto et al., 2013). Methionine and lysine are the most limiting AA in lactating cows (NRC, 2001), but supplementation of diets with crystalline methionine and lysine has been excluded because free methionine and lysine are quickly and almost totally degraded by the microorganisms in the rumen (NRC, 2001). In contrast, supplementing rumen-protected methionine (RPM) and rumen-protected lysine (RPL) has a positive effect on milk protein synthesis in dairy cows (Ordway, 2009; Osorio et al., 2013). Although the role of methionine in bovine embryonic development is unknown, there is evidence that methionine availability alters the follicular dynamics of the first dominant follicle (Acosta et al., 2017), the transcriptome of bovine preimplantation embryos in vivo (Penagaricano et al., 2013) and the embryonic lipid content (Acosta et al., 2016) which may serve as an energy substrate, improving embryo survivability.

Reproduction, Nutrition, and Health

A widespread assumption is that fertility of modern dairy cows is decreasing, particularly for Holstein-Friesen genetics, in part because of unintended consequences of continued selection for high milk production. This assumption has been challenged recently (Leblanc, 2010). There is a wide distribution of reproductive success both within and among herds. For example, within five California herds encompassing 6,396 cows, cows in the lowest quartile for milk yield in the first 90 days postpartum (32.1 kg/day) were less likely to have resumed estrous cycles by 65 days postpartum than cows in quartiles two (39.1 kg/day), three (43.6 kg/day) or four (50.0 kg/day); milk production did not affect risk for pregnancy (Santos et al., 2009). Changes in management systems and inadequacies in management may be more limiting for fertility of modern dairy cows than their genetics per se.

Dairy cows are susceptible to production disorders and diseases during the peripartal period and early lactation, including milk fever, ketosis, fatty liver, retained placenta, displaced abomasum, metritis, mastitis, and lameness (Mulligan et al., 2006; Roche et al., 2013). There is little evidence that milk yield per se contributes to greater disease occurrence. However, peak disease incidence (shortly after parturition) corresponds with the time of greatest negative energy balance (NEB), the peak in blood concentrations of nonesterified fatty acids (NEFA), and the greatest acceleration of milk yield. Peak milk yield occurs several weeks later. Disorders associated with postpartum NEB also are related to impaired reproductive performance, including fatty liver and ketosis (Mcart et al., 2012). Cows that lost > 1 body condition score (BCS) unit (1-5 scale) had greater incidence of metritis, retained placenta, and metabolic disorders (displaced abomasum, milk fever, ketosis) and a longer interval to first breeding than cows that lost < 1 BCS unit during the transition (Kim and Suh, 2003).

Indicators of NEB are highly correlated with lost milk production, increased disease and decreased fertility. However, the extent to which NEB is causative for peripartal health problems rather than just a correlated phenomenon must be examined critically. For example, in transition cows, inflammatory responses may decrease dry matter intake (DMI), cause alterations in metabolism and predispose cows to greater NEB or increased disease (Graugnard et al., 2012 and 2013). Inducing a degree of calculated NEB in mid-lactation cows similar to what periparturient cows often encounter, does not result in marked increases in ketogenesis or other processes associated with peripartal disease (Moyes et al., 2009). Nevertheless, early postpartal increases in NEFA and decreases in glucose concentrations were strongly associated with pregnancy at first insemination in a timed artificial insemination (TAI) program (Garverick et al., 2013). Although concentrations of NEFA and glucose were not different between cows that ovulated or did not before TAI, probability of pregnancy decreased with greater NEFA and increased with greater glucose concentrations at day three postpartum (Garverick et al., 2013). In support of these findings, early occurrence of subclinical ketosis is more likely to decrease milk yield and compromise fertility. Mcart et al. (2012) reported that cows with subclinical ketosis detected between three and seven days after calving were 0.7 times as likely to conceive to first service and 4.5 times more likely to be removed from the herd within the first 30 days in milk (DIM) compared with cows that developed ketosis at eight days or later.

Cows that successfully adapt to lactation and can avoid metabolic or physiological imbalance are able to support both high milk production and successful reproduction while remaining healthy. Decreased fertility in the face of increasing milk production may be attributed to greater severity of postpartal NEB resulting from inadequate transition management or increased rates of disease. Competition for nutrients between the divergent outcomes of early lactation and subsequent pregnancy will delay reproductive function. Because NEB interrupts reproduction in most species, including humans, inappropriate nutritional management may predispose cows to both metabolic disturbances and impaired reproduction. Cows must make “metabolic decisions” about where to direct scarce resources, and in early lactation, nutrients will be directed to milk production rather than to the next pregnancy.

Different nutritional strategies have been proposed to improve reproduction of the dairy cow with no detrimental effect on lactation performance. Feeding high quality forages, controlled-energy diets, or supplemental fat in the diet are some of the most common ways to improve energy intake in cows (Cardoso et al., 2013; Drackley and Cardoso, 2014). Reproduction of dairy cattle may benefit by maximizing DMI during the transition period, and minimizing the incidence of periparturient problems (Cardoso et al., 2013; Drackley and Cardoso, 2014).

▪ Prepartum Dietary Considerations

Controlling energy intake during the dry period to near calculated requirements leads to better transition success (Dann et al., 2005 and 2006; Janovick et al., 2011 Graugnard et al., 2012 and 2013). Cows fed even moderate-energy diets (1.50–1.60 Mcal NEL/kg DM) will easily consume 40–80% more energy (net energy of lactation; NEL) than required during both far-off and close-up periods (Dann et al., 2005 and 2006). Cows in these studies were all less than 3.5 BCS (1–5 scale) at dry-off and were individually fed a total mixed ration (TMR) based on corn silage, alfalfa silage, and alfalfa hay with some concentrate supplementation. We have no evidence that the extra energy and nutrient intake was beneficial in any way. More importantly, our data indicate that allowing cows to over-consume energy even to this degree may predispose them to health problems during the transition period if they face stressors or challenges that limit DMI (Cardoso et al., 2013).

Prolonged over-consumption of energy during the dry period can decrease post-calving DMI. Over-consuming energy results in negative responses of metabolic indicators, such as higher NEFA and beta-hydroxybutyrate (BHB) in blood and more triacylglycerol (TAG) in the liver after calving (Janovick et al., 2011). Alterations in cellular and gene-level responses in liver (Loor et al., 2006) and adipose tissue (Ji et al., 2012) potentially explain many of the changes at the cow level. Over-consumption of energy during the close-up period increases the enzymatic “machinery” in adipose tissue for TAG mobilization after calving, with transcriptional changes leading to decreased lipogenesis (fat synthesis), increased lipolysis (fat utilization) and decreased ability of insulin to inhibit lipolysis (Ji et al., 2012). Controlling energy intake during the dry period also improved neutrophil function postpartum (Graugnard et al., 2012) and so may lead to better immune function.

Allowing dry cows to consume more energy than required, even if cows do not become noticeably over-conditioned, results in responses that would be typical of overly fat cows. Because energy that cows consume in excess of their requirements must either be dissipated as heat or stored as fat, we speculated that the excess is accumulated preferentially in internal adipose (fat) tissue depots in some cows. Moderate over-consumption of energy by non-lactating cows for 57 days led to greater deposition of fat in abdominal adipose tissues (omental, mesenteric, and perirenal) than in cows fed a high-bulk diet to control energy intake to near requirements (Drackley et al., 2014). The NEFA and signaling molecules released by visceral adipose tissues travel directly to the liver, which may cause fatty liver, subclinical ketosis and secondary problems with liver function.

Data from our studies support field observations that controlled-energy dry cow programs decrease health problems (Beever, 2006). Other research groups (Holtenius et al., 2003; Vickers et al., 2013) have reached similar conclusions about controlling energy intake during the dry period, although not all studies have shown benefits (Winkleman et al., 2008). Application of these principles can be through controlled limit-feeding of moderate energy diets or ad libitum feeding of high-bulk, low-energy rations (Janovick et al., 2011; Ji et al., 2012).

Nutritionally complete diets must be fed and the TMR must be processed appropriately so that cows do not sort the bulkier ingredients. Feeding bulky forage separately from a partial TMR, or improper forage processing will lead to variable intake among cows, with some consuming too much energy and some too little. Underfeeding relative to requirements, where nutrient balance also is likely limiting, leads to increased incidence of retained placenta and metritis (Mulligan et al., 2006). Merely adding a quantity of straw to a diet is not the key principle; rather, the diet must be formulated to limit the intake of energy (approximately 1.3 Mcal NEL/kg DM, to limit intake to about 15 Mcal/day for typical Holstein cows) but meet the requirements for protein, minerals and vitamins. Reports of increased transition health problems or poor reproductive success with “low energy” dry cow diets must be examined carefully to discern whether nutrient intakes were adequate.

▪ Fresh Cow (postpartum) Dietary Considerations

Less is known about diet formulation for the immediate postpartum period to optimize transition success and subsequent reproduction. Increased research is needed in this area. Proper dietary formulation during the dry period or close-up period will maintain or enable rumen adaptation to higher grain diets after calving. Failure to do so may compromise early lactation productivity. For example, Silva-del-Rio et al. (2010) attempted to duplicate the dietary strategy of Dann et al. (2006) by feeding either a low-energy far-off diet for five weeks followed by a higher-energy diet for the last three weeks before parturition, or by feeding the higher-energy diet for the entire eight-week dry period. They found that cows fed the higher-energy diet for only three weeks before parturition produced less milk than cows fed the diet for eight weeks (43.8 vs. 48.5 kg/day). However, the far-off dry period diet contained 55.1% alfalfa silage and 38.5% wheat straw but no corn silage. In comparison, the higher-energy dry period diet and the early lactation diet both contained 35% corn silage. Ruminal adaptation likely was insufficient for cows fed the higher energy diet for only three weeks.

A major area of concern in the fresh cow period is the sudden increase in dietary energy density leading to subacute ruminal acidosis (SARA), which can decrease DMI and digestibility of nutrients. Adequate physical form of the diet, derived either from ingredients or mixing strategy, must be present to stimulate ruminal activity and chewing behavior, although good methods to quantify “adequacy” remain elusive. Dietary starch content and fermentability likely interact with forage characteristics and ration physical form. Dann and Nelson (2011) compared three dietary starch contents (primarily from corn starch) in the fresh cow period for cows fed a controlled energy-type ration in the dry period. Milk production was greatest when starch content was moderate (23.2% of DM) or low (21.0% of DM) in the fresh cow diet compared with high (25.5% of DM). If SARA decreases DMI and nutrient availability to the cow, NEFA mobilization and increased ketogenesis may follow. In addition, rapid starch fermentation in the presence of NEFA mobilization leads to bursts of propionate reaching the liver, which may decrease feeding activity and DMI according the hepatic oxidation theory (Allen et al., 2009). A moderate starch content (23-25% of DM) with starch of moderate fermentability (e.g., ground dry corn rather than high-moisture corn or ground barley) along with adequate effective forage fibre may be the best strategy for fresh cows. Recent research also has demonstrated that high grain diets can lead to greater numbers of gram-negative bacteria such as *E. coli* with resulting increases in endotoxin present in the rumen, which may decrease barrier function and inflammatory responses in the cow (Zebeli and Metzler-Zebeli, 2012).

Supplemental fats have been widely investigated as a way to increase dietary energy intake and improve reproduction. A novel strategy is to use polyunsaturated fatty acid (PUFA) supplements to improve reproduction (Silvestre et al., 2011). Cows fed calcium salts of safflower oil from 30 days before to 30 days after calving, followed by calcium salts of fish oil to 160 days postpartum, had greater pregnancy rates and higher milk production. The mechanism is believed to be provision of greater amounts of linoleic acid (omega-6 PUFA) until early postpartum, which improves uterine health, followed by greater amounts of omega-3 PUFA from fish oil to decrease early embryonic loss (Thatcher et al., 2011). The effects of turbulent transitions on reproduction are established early postpartum, likely during the first ten days to two weeks postpartum (Mcart et al., 2012; Garverick et al., 2013). By eight weeks postpartum, > 95% of cows should be at or above energy balance (Sutter and Beever, 2000). Use of targeted prepartum and postpartum strategies may minimize health problems and lessen NEB, and thereby improve subsequent fertility.

▪ The Importance of Amino Acids

Some AA are limiting for optimal milk production as evidenced by an increase in milk yield, and milk protein yield, and percentage after supplementation with specific, rumen-protected AA. The first two limiting AA for milk production are considered to be methionine and lysine (NRC, 2001). In addition, many AA can have positive effects on physiological processes that are independent of their effects on synthesis of proteins (Wu, 2013). Fertilization and the first few days of embryo development occur in the oviduct. By about five days after estrus the embryo arrives in the uterine horn. The embryo reaches the blastocyst stage by six to seven days after estrus. The embryo hatches from the zona pellucida by about day nine after estrus and then elongates on days 14–19. The elongating embryo secretes the protein interferon-tau that is essential for rescue of the corpus luteum and continuation of the pregnancy. By day 25–28 the embryo attaches to the caruncles of the uterus and begins to establish a vascular relationship with the dam through the placenta. During all the time prior to embryo attachment, the embryo is free-floating and is dependent upon uterine secretions for energy and the building blocks for development, including AA. Thus, it is critical to understand the changes in AA concentrations in the uterus that accompany these different stages of embryo development.

The lipid profile of oocytes and the early embryo can be influenced by the environment of the cow. Our group ran a trial to determine the effect of supplementing rumen-protected methionine on DNA methylation and lipid accumulation in preimplantation embryos of dairy cows (Acosta et al., 2016). Lactating Holsteins entering their 2nd or greater lactation were randomly assigned to two treatments from 30 ± 2 DIM to 72 ± 2 DIM: control (CON; n = 5, fed a basal diet with a 3.4:1 lysine:methionine) and methionine (MET; n = 5, fed the basal diet plus Smartamine M to a 2.9:1 lysine:methionine). Cows were superovulated (FSH) and embryos were flushed 6.5 days after artificial insemination. Embryos with stage of development four or greater were used for analysis. For lipids, fluorescence intensity of Nile Red staining was compared against a negative control embryo (subtraction of background). Thirty-seven embryos were harvested from cows (MET = 16; CON = 21). Cows receiving MET had greater lipid accumulation (7.3 arbitrary units) compared with cows receiving CON (3.7 arbitrary units). There were no treatment effects on numbers of cells or stage of development. In conclusion, cows supplemented with methionine produced embryos with higher lipid concentration compared with CON cows; this lipid could potentially serve as an important source of energy for the early developing embryo.

The requirements for complete development of bovine embryos have not yet been determined. Current culture conditions allow development of bovine embryos to the blastocyst stage (day 7-8) and even allow hatching of a percentage of embryos (day 9); however, conditions have not been developed in vitro that allow elongation of embryos. The methionine requirement for cultured pre-implantation bovine embryos (day 7-8) was determined in studies from University of Florida (Bonilla et al., 2010). There was a surprisingly low methionine requirement (7 µm) for development of embryos to the blastocyst stage by day seven; however, development to the advanced blastocyst stage by day seven appeared to be optimized at around 21 µm (Bonilla et al., 2010). Thus, the results of these studies indicated that development of morphologically normal bovine embryos did not require elevated methionine concentrations (>21 µm), at least during the first week after fertilization. Stella (2017) reported the plasma concentration of cows fed RPM or not (CON);it seems that cows fed RPM have plasma methionine concentration greater than 20 µm.

Researchers at the University. of Wisconsin (Toledo et al., 2015) conducted a trial with 309 cows (138 primiparous and 171 multiparous) that were blocked by parity and randomly assigned to two treatments: 1) CON: cows fed a ration formulated to deliver 2500 g of metabolizable protein (MP) with 6.9% lysine and 1.9% Met (as a % of MP) and 2) RPM: cows fed a ration formulated to deliver 2500 g of MP with 6.9% lysine and 2.3% Met (as a % of MP). Cows were randomly assigned to three pens with headlocks and fed a single basal TMR twice daily. From 28 to 128 DIM, after the morning milking, cows were headlocked for 30 minutes and the TMR of CON and RPM cows were individually top dressed with 50 g of distillers dried grains (DDG) or a mix of 29 g of DDG and 21 g of Smartamine M), respectively. Following a double Ovsynch protocol, cows were inseminated and pregnancy checked at 28 days (plasma Pregnancy Specific Protein-B concentration), and at 32, 47 and 61 days (ultrasound). Individual milk samples were taken once per month and analyzed for composition. There were no statistical differences in milk production, but milk from RPM cows had a higher protein concentration. Cows fed the methionine enriched diet tended ($P = 0.08$) to have a lower pregnancy loss from 28 to 61 days after AI (16.7 % CON cows vs. 10.0% in RPM cows). Pregnancy losses between days 28 and 61 were not different in the primiparous cows (12.8% CON and 14.6% RPM), however, pregnancy losses were lower ($P = 0.03$) in multiparous cows that received the methionine enriched diet (19.6% CON vs. 6.1% RPM; Toledo et al., 2017).

Perhaps the most detrimental impact of NEB on reproductive performance is delayed return to cyclicity. Dominant follicle (DF) growth and estradiol (E2) production are key factors for a successful conception, and their impairment can be attributed to reduced luteinizing hormone (LH) pulses and decreased circulating insulin and IGF-I concentrations (Komaragiri and Erdman, 1997). Furthermore, immune function is also suppressed during the periparturient period. Negative energy balance and fatty liver syndrome have been shown to impair peripheral blood neutrophil function (Hammon et al., 2006). Acosta et al. (2017) reported that methionine and choline supplementation induced a down regulation of pro-inflammatory genes, possibly indicating lower inflammatory processes in follicular cells of the first DF postpartum.

Additionally, supplementing methionine during the transition period increased 3β-hydroxysteroid dehydrogenase (3b-HSD) expression in the follicular cells of the first DF postpartum. Higher methionine concentrations in the follicular fluid of supplemented cows can potentially affect oocyte quality. Understanding how this may affect reproductive performance in commercial farms needs to be further investigated. Batistel et al. (2017) reported that studies with non-ruminant species argue for the potential relevance of the maternal methionine supply during late gestation in enhancing utero-placental uptake and transport of nutrients. The authors hypothesized that the greater newborn body weight from cows fed RPM compared with CON (42 vs. 44 kg) could have been a direct response to the greater nutrient supply from the feed intake response induced by methionine. The fact that certain AA and glucose induce motor signaling to different degrees is highly suggestive of ‘‘nutrient specific’’ mechanistic responses.

▪ Conclusions

Formulation and delivery of appropriate diets that limit total energy intake to requirements but also provide proper intakes of all other nutrients before calving can help lessen the extent of NEB after calving. Effects of such diets on indicators of metabolic health are generally positive, suggesting the potential to lessen effects of periparturient disease on fertility. Dietary supplementation of cows with methionine during the final stages of follicular development and early embryo development, until day seven after breeding, led to lipid accumulation changes in the embryos and resulted in differences in gene expression in the embryo. Methionine supplementation seems to impact the preimplantation embryo in a way that enhances its capacity for survival because there is strong evidence that endogenous lipid reserves serve as an energy substrate. The lower pregnancy losses from cows fed a methionine enriched diets suggest that methionine favors embryo survival, at least in multiparous cows.

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