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Controlling Energy Metabolism Through the Use of Feed Additives

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Introduction

Transition from the dry period to lactation is a challenging period for dairy cattle because of the many hormonal and metabolic changes that are taking place to support parturition and lactation. During this time, there is intense mobilization of fat stores to provide energy and precursors for milk synthesis. The liver serves as a critical organ in channeling the energy reserves from adipose tissue to mammary tissue. If nutrition of the dairy cow is not properly cared for, the liver can become overwhelmed with mobilized fat and energy-related metabolic disorders such as fatty liver and ketosis will occur. A leading researcher recently stated: "Since the late 1990's ketosis has emerged as the most important metabolic disease in dairy herd in the US, surpassing ruminal acidosis and milk fever in clinical significance" (Oetzel, 2007).

Many studies have been conducted to identify prefresh transition cow diets that can control energy metabolism and reduce the likelihood of fatty liver and ketosis. A recent review of that literature (Grummer, 2011) has indicated that altering the basal diet of prefresh transition cow diets may have limited potential to improve postpartum cow health, production, and reproduction. An alternative approach is to use feed additives to alter energy metabolism of the cow to avoid metabolic disorders. The objective of this paper is to review the biology of energy related metabolic disorders and feed additives that may be employed to improve energy metabolism and cow health and productivity.

Etiology of Fatty Liver and Ketosis and Strategies for Prevention

Fat is mobilized from adipose tissue as nonesterified fatty acids (NEFA). The greatest increase in blood NEFA and the greatest concentration of blood NEFA occurs near the time of calving and is a consequence of hormonal changes associated with calving, a reduction of feed intake at calving, and an increase in energy requirements to support lactation. After calving, NEFA concentration will decrease, but it will not reach the baseline achieved during the far-off dry period as long as the cow is in negative energy balance. The rate of decline in NEFA concentration after calving is dependent on the magnitude and duration of negative energy balance. Hepatic uptake of NEFA is dependent

on NEFA concentration in blood and the rate of blood flow to the liver. Both increase at and shortly after calving

Hepatic metabolism of NEFA is shown in Figure 1. Fatty acids can either be oxidized or esterified to glycerol to form triglyceride (TG). Fatty acids that are oxidized may be completely oxidized to carbon dioxide (CO_2) or partially oxidized to ketones. Fatty acids that are esterified can either be stored as TG or exported as a constituent of very low density lipoporotein (VLDL). Of the four metabolic fates of fatty acids, two are beneficial to the cow (complete oxidation and export as VLDL) and two are potentially detrimental (storage as TG and partial oxidation to ketones). Unfortunately, flux of fatty acids through the good pathways is limited. Complete oxidation of fatty acid occurs to provide energy (in the form of ATP) to hepatic cells. Liver cells only need a finite amount of ATP. It was once thought that glucose status was an important determinant of how much fatty acid was completely or partially oxidized, but that has been refuted (Drackley et al., 2001). Export of VLDL from the liver is an inherently slow process in ruminant animals such as the dairy cow (Kleppe et al., 1988). Because the "good" pathways essentially become saturated when there is excessive uptake of fatty acids by the liver, TG storage (i.e., fatty liver) and increased ketone formation (i.e., ketosis) are likely. Research from our lab (Cadorniga-Valino et al., 1997) and Iowa State University (Young et al., 1990) indicates that TG storage probably precedes ketone formation as "overflow" routes during excessive NEFA uptake by hepatic tissue. Fatty liver typically develops at calving while ketosis usually occurs a few weeks postcalving (Grummer, 1993).

Strategies to prevent fatty liver and ketosis focus on limiting fatty acid mobilization from adipose tissue or increasing the rate of VLDL export out of the liver. (There may be pharmaceutical agents to increase complete oxidation; however, none are approved. Even if they were, this would mean uncoupling oxidation from ATP production and generating heat, a wasteful process). Limiting fatty acid mobilization can be achieved by enhancing the energy balance of the cow or by chemically blocking mobilization. In general, attempts to enhance the energy balance of the cow have usually been through modification of the basal diet ingredients while chemical blockage of mobilization has usually been accomplished by addition of feed additives to the diet. The latter strategy is not favored because it fights "mother nature". Fatty acid mobilization is part of a homeorhetic process to support lactation. Why would we want to limit it, especially if one could increase export of VLDL from the liver? VLDL export from the liver is a favorable strategy because it enables delivery of fatty acids to the mammary gland (and other tissues) where they can be used as an energy sources or for synthesis of milk fat.

Management of Fatty Liver Syndrome and Ketosis via Feed Additives

Since the greatest rate of fat mobilization and infiltration into the liver occurs about the time of calving, strategies for prevention of fatty liver and ketosis should commence during the prepartum period. As described by Grummer (2011), alteration of the basal diet, particularly during the dry

period, may have limited potential to alleviate fatty liver and ketosis. Incorporation of feed additives into the diet may be a useful strategy. Monensin has been reviewed by others (Duffield and Bagg, 2000; Duffield et al., 2008) and will not be covered here other than to say that supplementation has been shown to lower blood ketones (Duffield and Bagg, 2000; Duffield et al., 2008), but not liver TG (Zahra et al., 2006; Chung et al., 2008).

An additive that enhances VLDL (i.e. TG) export out of the liver is preferred to one that chemically blocks lipid mobilization because it facilitates rather than inhibits a normal physiological process that supports lactation. Choline is the only feed additive with evidence that it enhances VLDL export from the liver and reduces liver TG and ketosis during the transition period.

Choline serves as a methyl donor in biochemical reactions and as a constituent of phosphatidylcholine (PC). Methionine serves as a methyl donor for choline synthesis; therefore, choline and methionine can spare the requirement of each other. Phosphatidylcholine can be synthesized from tri-methylation of phophatidylethanolamine or directly from choline. As a component of phospholipids, choline is essential for maintaining cell membrane structure and permeability, and for transport of lipid from the liver as a constituent of very low density lipoproteins (VLDL). Choline deficiency leads to fatty liver in laboratory animals.

Estimates of ruminal choline degradation are 80-98% (Atkins et al., 1988, Sharma and Erdman, 1989). Ruminal production of choline is negligible (Erdman, 1992). Protected choline supplements have been developed to decrease microbial degradation in the rumen and increase delivery of choline to the small intestine. Such products must provide for a low ruminal choline degradation rate **and** post ruminal release of choline from encapsulation to allow for absorption. There are several protected choline products on the market, however, very few have peer-reviewed research that documents their efficacy.

Protected choline (0, 45, 60, or 75 g Reashure/d, Balchem Corp.) was fed to transition dairy cows and a statistically non-significant reduction in liver TG was observed as level of supplementation was increased (Piepenbrink and Overton, 2004). Liver TG is a highly variable measurement in dairy cattle immediately after parturition and this study may not have had adequate animal numbers to detect statistically significant treatment differences. Therefore, our laboratory attempted to assess whether choline had a role in preventing or alleviating fatty liver using a less variable experimental model that employed energy restricted dry cows to induce fatty liver. Feeding 15 g choline/day in a ruminally protected form (60 g Reashure; Balchem Corp.) prevented induction of fatty liver and alleviated fatty liver following induction (Cooke et al., 2007). More recently, this same dose of protected choline (60 g Reashure; Balchem Corp.) was fed to dairy cows from 21 d prepartum to 6 wk postpartum and reduced liver TG during week 1 ($P = 0.04$) and week 3 ($P = 0.12$) postpartum (Zom et al., 2010).

If choline can prevent fatty liver, it should be able to reduce the incidence of ketosis. To evaluate effects on animal health parameters such as ketosis, trials employing large animal numbers are required and need to be conducted on large commercial farms. Lima et al. (2007) conducted two experiments on separate farms. On one farm, using 363 cows, 0 or 15 g/d of choline in a protected form (60 g/d Reashure, Balchem Corp.) was fed between 25 d prior to expected calving until 80 d post calving. Postpartum, DMI tended to be greater (23.9 vs. 22.6 kg/d; $P = 0.10$) and fat-corrected milk yield was greater (44.6 vs. 42.8; $P < 0.05$) for cows fed choline. Feeding choline reduced ($P < 0.05$) the incidence of ketonuria (10.7 vs. 28.8%), clinical ketosis (4.0 vs. 11.3%), and the relapse of clinical ketosis (2.3 vs. 6.85). On the second farm, the same treatments were fed only to heifers and the duration of treatment was only from 25 d prior to expected calving until calving. DMI and fat-corrected milk were not affected by treatment and choline supplementation tended to increase milk yield (28.7 vs. 27.9 kg/d; $P = 0.07$). Parameters related to ketosis were not affected by treatment. The absence of a response on the second farm may have been due to the absence of choline supplementation after calving, the use of heifers which are less susceptible to lipid-related metabolic disorders, or both.

Finally, if feeding rumen protected choline during the transition period improves liver and cow health, then one should expect to see an improvement in lactation performance. A summary of those studies is shown in Figure 2. In three of the studies (Janovick et al., 2006, Abeni et al., 2007, and Elek et al., 2008) methionine was estimated to be limiting; it was estimated to be in excess of requirements in the study of Piepenbrink et al. (2003). In every study, there was a positive response and in 6 of the 7 studies the response was statistically significant ($P < 0.10$) for either milk yield or milk yield corrected for energy content. Milk fat yield was increased in 5 of the 6 studies for which it was reported and milk protein yield was increased in 3 of the 6 studies for which it was reported. This data provides convincing evidence that protected choline positively affects lactation performance when feeding is initiated prior to calving and is continued during early lactation.

Chromium (Cr) is an essential nutrient for humans and animals. As a constituent of chromodulin, Cr has the potential to enhance the action of insulin. Insulin is antilipolytic, therefore, if Cr acts to potentiate its action, lipolysis should be reduced during supplementation. Therefore, Cr would act to counteract the cow's natural biology to become insulin resistant in an effort to support lactation. The obvious question is: why would one try to do that, particularly if protected choline is available to enhance fatty acid export out of the liver and prevent fatty liver and ketosis?

There have been numerous trials in which Cr has been fed to transition cows (Hayirli et al., 2001; Pechova et al., 2003; Smith et al., 2005, 2008; McNamara and Valdez, 2005; Sadri et al., 2009: Soltan, 2009). Milk production was increased in 4 of 6 studies with the increase being from 2.5 to 5.2 kg/day. Most of these studies were conducted with Cr-methionine which has not been approved for use in the United States. In the only study employing Cr-propionate (approved for

use in the US; McNamara and Valdez, 2005), the increase in milk yield was not significant during the time it was being supplemented (through 35 days in milk), but was significant for days 1-90 postpartum. Post partum dry matter intake also was increased in 4 of 6 studies; in two of the studies (McNamara and Valdez, 2005 and Soltan et al. 2009) there was evidence that the increase was not seen until after the transition period was over (> 35 days in milk). Blood NEFA has only been decreased postpartum in one of the five trials it was measured in (Soltan, 2009). Similarly, blood glucose has only been increased in one of five trials and it was decreased only at 4-5 weeks postpartum (Pechova et al., 2003). Postpartum insulin sensitivity, as measured by a glucose tolerance test, was only measured in one trial (Hayirli et al., 2001) and the results were conflicting. Glucose peak was decreased following the challenge (indicating increased sensitivity), but clearance rate of glucose from blood was decreased (indicating decreased sensitivity). Cr supplementation has not decreased liver triglyceride in the two studies it has been monitored (Hayirli et al., 2001; Smith et al., 2008). In summary, there is evidence that Cr supplementation increases dry matter intake and milk production, but there is little evidence it is acting through modification of insulin sensitivity during the transition period.

Niacin is also an antilipolytic compound at pharmacological doses. Niacin is a generic name; two forms exist: nicotinic acid and nicotinamide. Data in nonruminants indicates that nicotinamide is not antilipolytic, but rumen microbes can convert some nicotinamide to nicotinic acid. A large meta-analysis (Schwab et al., 2005) indicated that feeding free niacin has no effect on blood NEFA. This is because up to 98% is degraded in the rumen. Therefore, supplementation must be in a form protected from ruminal degradation. Very little research has been conducted on feeding rumen-protected niacin on transition cows. Two recent studies indicated that 12 (Yuan, 2011) or 24 (Morey et al., 2009) g niacin/day (in a protected form, NiaShure, Balchem Corp.) starting at 21 d before calving can reduce peak blood NEFA on the day of calving. Liver TG immediately after calving was not significantly decreased in either study, however, in one study (Yuan, 2011) it was reduced approximately 50 %.

Conclusions

Feed additives can help control energy metabolism and metabolic disorders. Increasing fat export out of the liver is preferred because it facilitates fatty acid mobilization and delivery of fatty acids to the mammary gland to support milk synthesis. Use of feed additives should begin prepartum so that the surge in blood NEFA at calving can be managed and continue postpartum to aid the cow during continued high NEFA resulting from negative energy balance.

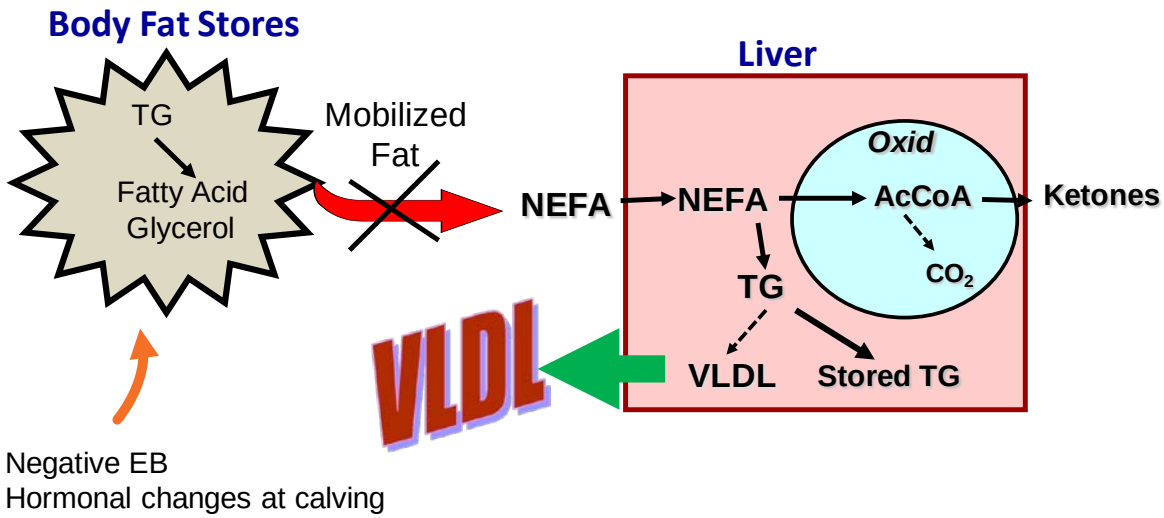

Figure 1. Lipid mobilization and hepatic fatty acid metabolism. Dotted lines indicate important routes of fatty acid disposal that can become saturated during intense periods of lipid mobilization. Strategies to prevent fatty liver syndrome and ketosis include blocking fatty acid mobilization from adipose tissue and enhancing VLDL export.

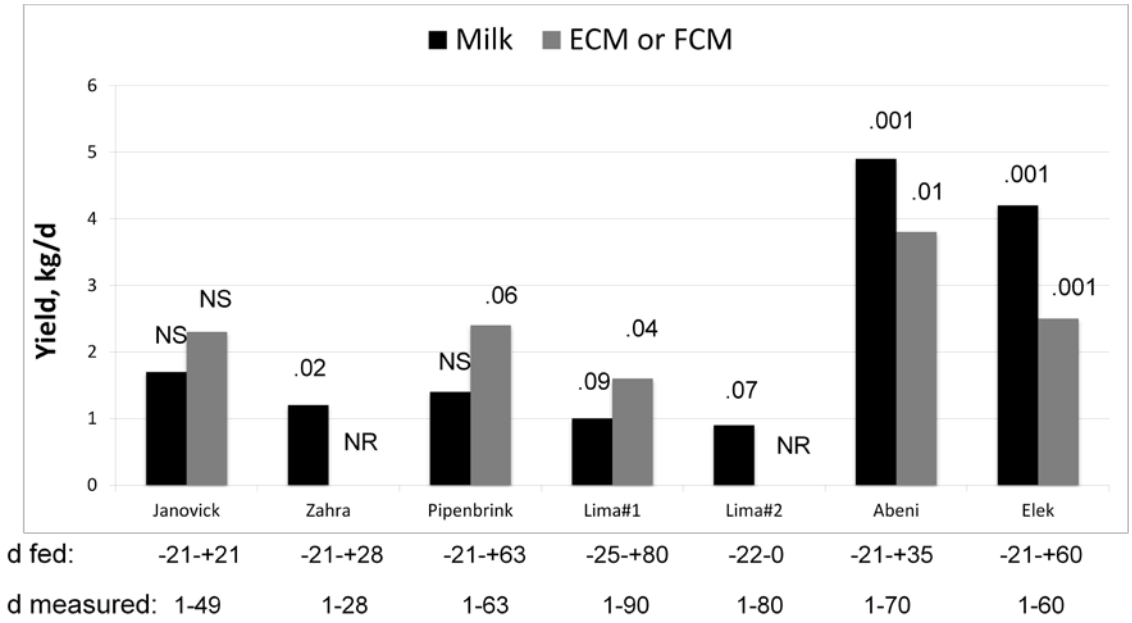

Figure 2. Milk and energy-corrected milk or fat-corrected milk production response by cows fed protected choline during the transition period (Abeni et al., 2007; Elek et al., 2008; ; Lima et al., 2007; Janovick Guretzky et al., 2006; Zahra et al., 2006; Piepenbrink and Overton, 2003). NS = Nonsignificant response, NR = Not reported. Dietary methionine was predicted to be limiting in the Janovick, Abeni, and Elek studies and predicted to be in surplus in the Piepenbrink study.

References

1. Abeni, F., M. Speroni, M. G. Terzano, L. Migliorati, P Cavassini, and G. Pirlo. 2007. Effects of rumen protected choline on production responses in Italian Friesian dairy cows. J. Dairy Sci. 90(Suppl. 1):354.
2. Atkins, K.B., R. A. Erdman, and J. H. Vandersall. 1988. Dietary Choline effects on milk yield and duodenal choline flow in dairy cattle. J. Dairy Sci. 71:109-116.
3. Cadorniga-Valino, C., R. R. Grummer, L. E. Armentano, S. S. Donkin, and Sandra J. Bertics. 1997. Effects of fatty acids and hormones on fatty acid metabolism and gluconeogenesis in bovine hepatocytes. J. Dairy Sci. 80:646-656.
4. Chung, Y., M. M. Pickett, T. W. Cassidy, and G. A. Varga. 2008. Effects of prepartum dietary carbohydrate source and monensin on periparturient metabolism and lactation in multiparous cows. J. Dairy Sci. 91:2744-2758.
5. Cooke, R. F., N. S. Del Rio, D. Z. Caraviello, S. J. Bertics, M. H. Ramos, and R. R. Grummer. 2007. Supplemental choline for prevention and alleviation of fatty liver in dairy cattle. J. Dairy Sci. 90:2413-2418.
6. Drackley, J. K., T. R. Overton, and G. N. Douglas. 2001. Adaptations of glucose and long-chain fatty acid metabolism in liver of dairy cows during the periparturient period. J. Dairy Sci. 84(E. Suppl.):E100-E112.
7. Duffield, T., A. R. Rabiee, and I. J. Lean. 2008. A meta-analysis of the impact of monensin in lactating dairy cattle. Part 1. Metabolic effects. J. Dairy Sci. 91:1334-1346.
8. Duffield, T., and R. Bagg. 2000. Use of ionophores in lactating dairy cattle: A Review. Can. Vet. J. 41:388-394.
9. Elek, P., J. R. Newbold, T. Gaal, L. Wagner, and F. Husveth. 2008. Effects of rumen-protected choline supplementation on milk production and choline supply of periparturient dairy cows. Animal 2:1595-1601.
10. Erdman, R. A. 1992. Vitamins. Pages 297-308 in Large Dairy Herd Management. H. H. Van Horn and C. J. Wilcox, eds. American Dairy Science Association, Champaign, Il.
11. Grummer, R. R. 2011. Managing the Transition Cow-Emphasis on Ketosis and Fatty Liver Syndrome. Proceedings from the Virginia Feed Association Conference. Virginia Tech University, Roanoke, VA.
12. Grummer, R. R. 1993. Etiology of lipid related metabolic disorders in periparturient dairy cattle. J. Dairy Sci. 76:3882-3896.
13. Hayirli, A., D. R. Bremmer, M. T. Socha, and R. R. Grummer. 2001. Effect of chromium supplementation on production and metabolic parameters in periparturient dairy cows. J. Dairy Sci. 84:1218-1230.
14. Janovick, N. A., and J. K. Drackley. 2010. Prepartum dietary management of energy intake affects postpartum intake and lactation performance by primiparous and mulitparous Holstein cows. J. Dairy Sci. 93:3086-3102.

15. K. Yuan. 2011. Effects of rumen-protected niacin on transition and lactating dairy cows during the summer in Wisconsin. M.S. Thesis, Univ. Wisconsin-Madison.
16. Kleppe, B. B., A. J. Aiello, R. R. Grummer, and L. E. Armentano. 1988. Triglyceride accumulation and very low density lipoprotein secretion by rat and goat hepatocytes in vitro. J. Dairy Sci. 71:1813.
17. Lima, F. S., M. F. Sa Filho, L. F. Greco, F. Susca, V. J. A. Magalhaes, J. Garrett, and J. E. P. Santos. 2007. Effects of feeding rumen-protected choline (RPC) on lactation and metabolism. J. Dairy Sci. 90(Suppl. 1):174.
18. McNamara, J. P., and F. Valdez. 2005. Adipose tissue metabolism and production responses to calcium propionate and chromium propionate. J. Dairy Sci. 88:2498-2507.
19. Morey, S. D., B.J. Bradford, L.K. Mamedova, and D. E. Anderson. 2009. Effects of encapsulated niacin on metabolism and production of periparturient dairy cows. J. Dairy Sci. 92(E-Suppl. 1):519.
20. Oetzel, G. R. 2007. Herd-level ketosis – diagnosis and risk factors. Preconference Seminar 7C. 40th Annual Conf. Amer. Asssoc. Bovine Pract. Vancouver, BC, Canada.
21. Pechova, A. A. Podhorsky, E. Lokajava, L. Pavlata, and J. Illek. 2002. Metabolic effects of chromium supplementation in dairy cows in the peripartal period. Acta Vet. Brno 71:9-19.
22. Piepenbrink, M. S., and T. R. Overton. 2003. Liver metabolism and production of cows fed increasing amounts of rumen-protected choline during the periparturient period. J. Dairy Sci. 86:1722-1733.
23. Sadri, H., G. R. Ghorbani, H. R. Rahmani, A. H. Samie, M. Khorvash, and R. M. Bruckmaier. 2009. Chromium supplementation and substitution of barley grain with corn: Effects on performance and lactation in periparturient dairy cows. J. Dairy Sci. 92:5411-5418.
24. Sharma, B. K., and R. A. Erdman. 1989. Effects of dietary and abomasally infused choline on milk production responses of lactating dairy cows. J. Nutr. 119:248-254.
25. Smith, K. L., M. R. Waldron, J. K. Drackley, M. T. Socha, and T. R. Overton. 2005. Performance of dairy cows as affected by prepartum dietary carbohydrate source and supplementation with chromium throughout the transition period. J. Dairy Sci. 88:255-263.
26. Smith, K. L., M. R. Waldron, L. C. Ruzzi, J. K. Drackley, M.T. Socha, and T. R. Overton. Metabolism of dairy cows as affected by prepartum dietary carbohydrate source and supplementation with chromium throughout the periparturient period. J. Dairy Sci. 91:2011-2020.
27. Soltan, M. A. 2009. Effect of dietary chromium supplementation on productive and reproductive performance of early lactating dairy cows under heat stress. J. Anim. Phys. and Anim. Nutr. 94:264-272.
28. Young, J. W., J. J. Veenhuizen, J. K. Drackley, and T. R. Smith. 1990. New insights into lactation ketosis and fatty liver. Page 60 in Proc. 1990 Cornell Nutr. Conf. Feed Manufact., Cornell Univ., Ithaca, NY.

29. Zahra, L. C., T. F. Duffiled, K. E. Leslie, T. R. Overton, D. Putnam, and S. J. LeBlanc. 2006. Effects of rumen-protected choline and monensin on milk production and metabolism of periparturient cows. J. Dairy Sci. 89:4808-4818.
30. Zom, R., J. van Baal, M. J. de Veth, R. M. A. Goselink, H. C. A. Widjaja-Greefkes, J. A. Bakker, and A. M. van Vuuren. 2010. Effects of rumen-protected choline on performance and hepatic fat metabolism in periparturient dairy cattle. J. Dairy Sci. 93(E-Suppl. 2):781. Abstr.