Prepartum Nutrition: The Key to Diagnosis and Management of Periparturient Disease

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Introduction

Periparturient diseases are the scourge of the dairy industry. Economic loss from decreased milk production is only the tip of the proverbial iceberg in evaluating total disease losses. Not only is there milk lost following disease diagnosis and treatment, recent work has shown that 30% of total milk losses from a left displaced abomasum (LDA) occur prior to diagnosis.[1] Milk losses prior to disease diagnosis were also found for metritis and ketosis.[2] Contrary to popular belief, high milk production does not predispose the cow to periparturient diseases, except possibly milk fever.[3] Investigators from Cornell estimated financial losses associated with various periparturient disease problems. Total losses from lost and discarded milk, veterinary fees, increased labor, pharmaceuticals and premature culling ranged from $145 per case of ketosis to $340 for a LDA case.[4] Suggested costs associated with milk fever were $334 per case and $285 per case for retained placenta.[4] Survey data from Ontario suggest that slightly over 50% of all lactations are affected by at least one periparturient disease, suggesting substantial economic loss from these diseases.[5] Unfortunately, periparturient diseases generally do not occur as single entities.

Epidemiologic studies using path analysis have shown periparturient health disorders not to be totally independent events, but rather a complex of interrelated disorders. Path analysis has shown that if a cow succumbs to milk fever she is 4 times more likely to also have a retained placenta[6] and 2.3 times more likely to have a LDA.[7] Being afflicted with retained placenta increases the probability of ketosis incidence by 16.4 times.[6] Cows with a LDA are 1.8 times more likely to have another disease, especially milk fever, retained placenta or ketosis.[1] It is doubtful that this is new information to any dairy producer or practitioner. Clearly the premise that if a cow makes it through the transition period free of disease problems, one can expect a fairly productive lactation period with high hopes of efficient reproductive performance. These relationships underscore the critical importance of periparturient disease prevention as a goal for improving productive efficiency.

So with these diseases occurring during the early lactation period, why focus on the dry cow diet? The late gestation diet has been shown to play a critical role in modulating a cow's predisposition to periparturient health disorders.[6,8] Specific nutrient imbalances in the diet of late gestation cows have been related to increased prevalence of milk fever, hypomagnesemic tetany, retained placenta, downer cow syndrome, mastitis, udder edema, ketosis, hepatic lipidosis and displaced abomasum. A summary of dry cow dietary imbalances (nutrient deficiency or excess) and potential resulting disorder are compiled in Table 1. Why does the prepartum diet have

Table 1. Prepartum dietary nutrient imbalances (deficiency or excess) and their associated predisposition to periparturient metabolic and reproductive disorders.[1]

POTENTIAL DISEASE PROCESS	NUTRIENT STATUS[2]		ASSOCIATED DISEASE[4]
	Deficiency[3]	*Excess*	
Dystocia	Energy, Protein	Energy	MF, FCS
Milk Fever	Ca, Mg, Protein	Ca, P, Na, K, Vit D, Energy(?)	DYST, RP, KET, MAST, LDA(?)
Hypomagnesemic Tetany	Mg	K, Protein	MF(?)
Downer Cow Syndrome	P, K(?)	Protein, K	MF, FCS
Retained Placenta	Se, Vit E, Vit A, Cu, I, P, Protein, Energy	Energy, K	FCS, MF, KET
Delayed Uterine Involution/Metritis	Ca, Co, Vit D, Se, Vit E(?)	Energy	RP, FCS, LDA(?)
Mastitis	Se, Vit E, Vit A	------	MF, LDA
Udder Edema	Protein, Mg	Na, K, Energy(?)	MAST(?)
Ketosis	Protein, Energy	Energy(?)	MF, RP, LDA, FCS
Displaced Abomasum	Ca(?), Fiber (Forage)	Energy (Grain)	MET, MAST, MF, KET

[1]Adapted from reference 19.

[2]Relative to recommended NRC (1988) nutrient requirements. (?) signifies an uncertain association based on data from the literature.

[3]Either an absolute or induced deficiency state. Induced deficiency results from excess levels of interfering nutrients reducing bioavailability of the nutrient of concern.

[4]Concurrent or predisposing condition as compiled from the literature. Disease abbreviations: dystocia (DYST); milk fever (MF); retained placenta (RP); ketosis (KET); metritis (MET); mastitis (MAST); left displaced abomasum (LDA); and fat cow syndrome (FCS).

such an impact on disease susceptibility? To fully appreciate the role of prepartum nutrition on metabolic incidence, one needs to understand the tremendous metabolic changes which take place during late gestation in preparation for impending lactation and how diet may influence these changes. The objectives of this presentation are: first, present an overview of maternal metabolic changes necessary to transition from pregnancy into lactation; second, discuss the role of prepartum energy, protein and mineral nutrition and how this impacts on metabolic disease incidence; and third, present a modified method of assessing the role of nutritional status in metabolic disease problems.

Late Gestational Metabolism

Nutrient requirements for the late pregnant, nonlactating cow are only slightly higher than maintenance, approximately equivalent to energy and protein required to produce 9-15 lb of 4% milk per day.[9] When one compares daily requirements for glucose, amino acids, fatty acids and calcium for either a lactating (4 days postpartum; 65 lbs milk, 4.7% fat and 4.2% protein) or pregnant cow, lactational requirements are 2.7, 2.0, 4.5 and 6.8 times greater than those needed for pregnancy, respectively.[10] These differences represent changes in nutrient requirements over a period of only a few days and highlight the tremendous metabolic alterations necessary to adequately support lactation. If these metabolic changes are not effectively enacted, metabolic disease and infertility problems may result.

Fetal Metabolism

Glucose is the primary nutrient required by both mammary gland and gravid uterus for metabolism. The mammary gland converts glucose to lactose while the gravid uterus oxidizes glucose as its primary metabolic fuel. Oxidation of glucose, lactate and amino acids account for most of the energy utilization by the gravid uterus.[10] Other potential energy substrates for the cow include acetate, fatty acids and ketone bodies. These substrates, however, are not appreciably oxidized for energy by the gravid uterus as a result of their failure to be significantly transported across the placenta from maternal circulation.[10,11] Glucose and lactate are transported across the placenta by facilitated diffusion, while amino acids are actively transported.[10] This results in fetal glucose being totally dependent upon maternal concentrations in contrast to fetal amino acids concentrations being consistently greater than maternal levels.[10,11] Complete oxidation of glucose and lactate can only account for 50 to 60% of the total fetal caloric requirement.[10] This suggests amino acids account for 30 to 40% of the total conceptus caloric requirement in addition to providing the necessary substrate to support substantial protein synthesis activity.[10,11]

In periods of maternal undernutrition, the fetus has little flexibility in terms of available alternative metabolic fuels. Fetal glucose and lactate concentrations and utilization decline, a direct result of declining maternal concentrations. In contrast, fetal amino acid uptake is essentially unaffected by maternal nutrient status, suggesting a greater role for amino acids in fetal energy production (Table 2). A study using pregnant sheep showed amino acid oxidation, based on urea synthesis rates, to increase from 32% to 60% of total fetal oxygen consumption for diets either maintaining or restricting maternal nutrient intake throughout gestation, respectively.[12] These data clearly demonstrate that amino acids are essential fetal energy substrates, especially during periods of maternal undernutrition and places an additional protein utilization burden on the dam. A study investigating nutritional effects of feeding diets containing equal energy but differing in protein content (8 - 12 - 15% CP) to twin-pregnant ewes between day 110 to 140 of gestation found ewes fed low protein had a 18% reduction in fetal weight compared to the higher protein diets.[13] Fetal weights were not different between the 12 and 15% protein diets. These data suggest there exists some capacity for the placenta to sustain amino acid delivery to the fetus, but it is not unlimited. Relative to this capacity to deliver amino acids, where do they come from? No protein serves as an amino acid reserve tissue. Ewes receiving either 8 or 12% protein diets both lost maternal skeletal protein, whereas ewes on the 15% protein diet gained carcass protein mass. Mobilization of maternal skeletal protein ("labile protein") can explain why birth weight is not dramatically affected within reasonable variation in maternal nutritional status, at the expense of maternal protein mass. Prepartum loss in maternal nutrient reserves or body protein may have severe detrimental impact on health, lactation and reproductive performance following parturition since these nutrient pools are critical to support early lactational nutrient losses.

Table 2. Placental transport of potential fetal energy substrates and their contribution to total energy requirement under adequate and inadequate maternal nutrient status.[1]

Substrate	Placental Transport		Maternal Nutritional Status	
	Method	Efficiency	Adequate	Inadequate
Glucose, Lactate	Diffusion	High	50 - 60%	20-30%
Amino Acids	Active Transport	High	30 - 40%	>60%
Acetate	Diffusion	Moderate-Low	10 - 15%	< 5%
Ketones	Diffusion	Low	< 1%	< 1%
NEFA	Diffusion	Low	< 1%	< 1%

[1]Adapted from data presented in references 10 and 11.

Maternal Metabolic Adaptations

Maternal metabolic adaptations occur in many nonreproductive tissues in a coordinated way to support pregnancy and prepare for lactation. These are the metabolic regulatory processes associated with homeorrhesis as described by Bauman and Currie.[14] Tissues of primary homeorrhetic concern are adipose, skeletal muscle and liver. Metabolic changes associated with the transition from pregnancy to lactation take place in all animals including those that are well-fed. However, these metabolic changes may become exaggerated when maternal supplies of energy, protein or both are inadequate, thus leading to metabolic disease problems.

Given that glucose is the primary energy substrate for both gravid uterus and mammary gland, maternal metabolic processes need to designate more glucose for these purposes. Increasing glucose availability to reproductive tissues is accomplished by reducing glucose utilization by maternal nonreproductive tissues and increasing availability of gluconeogenic precursors. In order to set aside more glucose, maternal tissues need to have an alternative energy substrate available. Alternate maternal energy substrates are nonesterified fatty acids (NEFA) and ketone bodies. In order to provide NEFA, adipose tissue needs to switch from a mode of fat deposition (lipogenesis) to fat mobilization (lipolysis). Lipolysis is stimulated by making adipocytes less responsive to insulin and more responsive to ß-adrenergic agonists, like epinephrine.[10,14] Insulin is the metabolic regulator responsible for promoting lipogenesis and suppressing lipolysis in addition to facilitating tissue uptake of glucose. During late pregnancy and through early lactation there is a gradual increase in insulin resistance of maternal nonreproductive tissues coupled with a greater sensitivity of adipocytes to adrenergic stimulation. These changes facilitate increased availability of NEFA and glucose for maternal and fetal tissues, respectively. Gradual increases in serum NEFA concentrations during late gestation through early lactation document this metabolic conversion from lipogenesis to lipolysis. Lipolysis can be greatly exaggerated in pregnant cows being underfed or pregnant with twins. Exaggerated lipolysis results in greatly elevated serum NEFA concentrations which potentiates excessive hepatic lipid accumulation, a prerequisite to many periparturient disease problems.[15,16,17]

Relative to maternal carbohydrate and protein metabolism during the transition period, metabolic adaptations stimulate gluconeogenesis to facilitate availability of glucose. Primary substrates for gluconeogenesis include amino acids from diet or protein catabolism and glycerol from lipolysis. Since there is no reserve pool of available amino acids, the primary source of amino acids comes from skeletal muscle catabolism.[10] This brings up the concept of a "labile protein pool", which at times has thought either not to exist or be of minimal size to be metabolically significant. Calculations of net nutrient balance in early lactation show mammary gland glucose needs to exceed glucose availability, thus necessitating mobilization of amino acids to support lactational demands. Magnitude of this metabolizable protein deficit is approximately 500 g/day.[10] Given this labile protein pool is fairly small, mobilization of any protein prepartum may have serious detrimental metabolic effects during the postpartum period. Twin pregnant sheep fed gestational diets of 8 and 12% protein experienced significant losses of nitrogen from maternal carcass tissue compared to 15% protein diets.[13] Interestingly, 12% crude protein is the NRC recommended dietary protein level for ewes with twin pregnancy.[18] Similarly, others have suggested the NRC protein requirement for pregnancy in dairy cattle is also low, not accounting for maternal labile protein utilization.[19,20]

In conjunction with increased need for gluconeogenesis to meet increasing glucose needs and in contrast to protein catabolism in other tissues, hepatic protein synthesis is stimulated during the transition period.[10] Increased hepatic protein synthesis would be expected to help sustain increased gluconeogenesis and lipid metabolism necessary to support impending lactation.

Prepartum Nutrition and Metabolic Disease

In appreciating what a high producing cow needs to metabolically accomplish during the transition period, one has to wonder why there are not more problems with periparturient diseases. As a cow approaches calving, it is absolutely essential that she continues to receive her entire daily allotment of required nutrients to prevent perturbing metabolic adaptations and predisposing the cow to periparturient disease. Cows which experienced periparturient disease have been shown to have a greater decline in dry matter intake (DMI) prepartum than unaffected cows.[21,23]

Unfortunately, it has been well documented that DMI normally declines to some degree in late gestation.[19,20,23] The decline in DMI in late gestation varies somewhat in its timing prior to parturition and severity. An interplay of various physiologic (i.e., physical distention) and metabolic (i.e., hormone and metabolite concentrations) factors primarily regulate intake capacity. However, other factors including diet composition (i.e., effective fiber, fiber quality), pregnancy status (twins vs. single), social interactions and environmental conditions (i.e., heat stress) may further influence actual DMI in late pregnancy. Observed DMI for primiparous and multiparous cows are presented in Table 3. Based on the DMI intake changes over the dry period,

Table 3. Suggested mean (± standard deviation) dry matter intake (DMI) for late pregnant dairy cattle by pregnancy stage and status.[1]

	DMI Units	PREGNANCY STAGE	
		EARLY DRY[2]	CLOSE-UP DRY[2]
Heifers[3]	lb/d	22.4 ± 1.7	19.3 ± 3.1
	% BW[4]	1.85 ± 0.2	1.49 ± 0.2
Mature Cows[4]	lb/d	33.8 ± 5.2	29.5 ± 6.6
	% BW	2.06 ± 0.3	1.73 ± 0.4
Twin Pregnancy[4]	lb/d	29.5 ± 4.6	24.2 ± 5.0
	% BW	1.88 ± 0.3	1.49 ± 0.3

[1]Adapted from reference 27.

[2]Early Dry period is defined as 4 - 6 weeks after dry off. Close-up Dry period is defined as 2 - 4 weeks prior to calving.

[3]Data compiled from 20 singleton pregnant heifer Holstein cattle with an average live pregnant body weight of 1244 lbs.

[4]Data compiled from 38 singleton pregnant, mature Holstein cattle with an average live pregnant body weight of 1650 lbs and 6 twin pregnant, mature Holstein cows with an average live pregnant body weight of 1580 lbs.

increasing nutrient density in the later gestation period would be warranted to compensate for the decline in DMI in order to effectively maintain delivery of nutrients.

From these data it is also interesting to note the lower DMI associated with multiparous cows having a twin pregnancy. Besides overall lower DMI, intake starts to decline at 5 rather than 3 weeks prior to calving in cows having either twins or single calf, respectively.[24] This seems contradictory given higher conceptus and overall nutrient requirements for twin pregnancy compared to single pregnancy. Yet these data may shed some light on why cows with a twin pregnancy have greater incidence of periparturient diseases. Cows pregnant with twins experience more severe negative nutrient balance during the prepartum period resulting in exaggerated lipid mobilization, increased hepatic lipid infiltration and greater labile protein depletion prepartum. This combination of metabolic responses may account for the observed increase in metabolic disease susceptibility of twin-pregnant cows.

Dietary Energy

Energy density of the late gestation diet has swung from one extreme to the other. Reports linking excessive energy intake with "fat cow syndrome" and subsequent increased disease problems resulted in a marked response to decrease prepartum energy intake.[25] Consequently, field observations have suggested an overreaction to prepartum energy resulting in cows freshening with insufficient amounts of body condition, aptly termed "thin cow syndrome". A question to be raised is whether or not the current NRC recommendation for dietary energy is sufficient. Recent studies using different methodologies in Holstein cattle have confirmed that pregnancy requirements are consistent with current energy recommendations.[26,27] However, the current energy model is not adequate to meet the energy needs of a cow pregnant with twins.[24]

At issue with energy nutrition of the pregnant cow is maintaining adequate energy intake in the face of declining DMI. Force feeding late pregnant cows to overcome DMI reduction resulted in lower lipid infiltration of the liver and improved postpartum DMI and milk component yields compared to cows which were allowed to experience DMI reduction.[23] Adding fermentable carbohydrates to the late gestation diet can have positive effects from increasing dietary energy density and initiating rumen mucosa adaptation to a grain diet. Feeding other gluconeogenic precursors such as propylene glycol has also shown positive effects on energy status of the late pregnant cow.[20] Feeding of fat in the prepartum diet has been advocated to improve energy status and prevent hepatic lipid infiltration; however, research evidence of a positive effect has been equivocal.[20] The overall goal during the dry period is to maintain energy status, i.e., body condition, and to prevent body condition loss. Cows dried off in lower condition may be appropriately managed to gain some condition during the dry period. This may be less efficient that during late lactation, but at issue here is not efficiency but adequacy of reserves and postpartum metabolic consequences.

For the dairy practitioner, primary concerns in managing late pregnant cows are ensuring adequate changes in dietary energy density and maximizing DMI during the transition period. Too maximize DMI, one needs to identify and minimize those factors which can potentially decrease DMI. Relative to the diet, one should focus on fiber amount and quality. Poor quality forages with low rates of fermentation can further accentuate DMI suppression in late gestation. Nondietary factors such as environmental conditions, feed availability, bunkspace, animal social interactions, cow condition score and stress levels all should be critically evaluated as potential issues having an impact on feed intake.

Dietary Protein

Although energy seemingly plays a major role in late gestation nutrition, data presented above points more toward a critical role of protein nutrition. Additional undegradable protein fed during late gestation improved body condition at calving in dairy heifers and beef cattle.[28,30] Using path analysis and logistic regression, it was found that feeding dietary protein higher relative to NRC recommendations 3 weeks prepartum reduced uncomplicated ketosis and retained placenta incidence.[6] Mature Holstein cows fed higher amounts of undegradable protein prepartum had significantly reduced incidence of clinical ketosis and reduced days open

compared to cows receiving a similar diet containing lesser protein amount.[31] Increasing prepartum dietary undegradable protein content improved glucose status in cows and tended to decrease NEFA concentrations, suggesting a possible effect on ketosis incidence.[32] Cows fed a higher protein prepartum diet, independent of energy content, had lower serum NEFA concentration, NEFA to cholesterol ratio, and fatty liver score.[15] Cows afflicted with either ketosis or LDA were found to have lower serum apoproteins associated with very low density lipoprotein (VLDL) structures, suggesting an inability of the liver to export triglycerides.[33] These studies emphasize the critical role of amino acids in maintaining glucose homeostasis and fat metabolism during the transition period.

Clinical responses to supplemental protein circumstantially suggest current recommendations for dietary protein during pregnancy are being underestimated. Prepartum protein deficiency may then result in depletion of the labile protein pool to support gestation rather than early lactation when gluconeogenesis is critically needed. Prepartum protein depletion adversely affects periparturient metabolic status, resulting in greater incidence of ketosis, hepatic lipidosis and other metabolic diseases. Subsequent lactation and reproductive performance may also be impaired either directly as a result of limited amino acid availability or indirectly as a result of metabolic disease.

Until recently, there has not been any study specifically determining conceptus compositional changes during gestation for today's Holstein cow. This study found protein accretion in the gravid uterus during late gestation was consistent with current NRC dietary protein recommendations.[26] However, this study addressed only conceptus protein accretion and was not able to assess protein maintenance or efficiency of utilization issues. Based on data from beef cattle and sheep, efficiency of utilization of metabolizable protein for pregnancy was thought to be 50%.[10] This is in sharp contrast to the well established efficiency of metabolizable energy utilization of 12.5%.[34] Calculations using more recent nitrogen balance data in pregnant beef cows suggests an efficiency value of less than 33%, which would increase current metabolizable protein recommendations by 50%.[10] These data need further substantiation but, lend credence to the clinical response studies.

At present many practitioners are recommending higher than recommended dietary protein concentrations to pregnant cows. As discussed above relative to DMI declines during the close up dry period, dietary protein content will need to be appropriately adjusted. However, excessive dietary protein content (>16% CP) should not be generally recommended as its negative impact on energy balance in excreting excess urea. One study feeding higher levels of protein (15%), all from rumen degradable sources, reported a 66% incidence of downer cow syndrome with high death loss compared to a lower protein (8%) diet.[35] Another issue to be addressed is distribution of dietary crude protein into soluble, degradable and undegradable fractions. Most studies with improved animal performance from increased prepartal dietary protein have used additional undegradable protein sources. These responses may be a result of improved protein status or a specific limiting amino acid; this has not been well defined. Clearly further research is necessary for us to better understand rumen dynamics during pregnancy and its effects on microbial energy utilization and protein production.

Macrominerals

A periparturient disease most frequently associated with macromineral nutrition is parturient hypocalcemia or milk fever. Milk fever is a rather nasty periparturient disease problem as a result of its association with 8 other periparturient disease processes and its negative effect on postpartum DMI.[36] Following decades of milk fever research, the underlying pathogenesis has been related to a failure of the calcium homeostatic system to maintain blood calcium concentrations with the onset of lactation. Kidney and bone are the target organs of concern which are unresponsive to parathormone stimulation. A number of prepartum dietary factors have been identified as influencing this target organ responsiveness; however, there is no consensus on predisposing factor(s) and mode of prevention.

Prepartum dietary amounts of calcium and phosphorus and their ratio were first considered as primary determinants of milk fever.[37] Subsequent research showed that extremely low dietary calcium (<20 gm/day) could eliminate the problem, but these diets were not practical with available feedstuffs.[38,39] Further work has shown a role for magnesium in calcium homeostasis and subsequently, milk fever problems.[40,41] Practitioners have recognized a transition from classic "textbook" milk fever cases responsive to calcium gluconate infusion alone, to milk fever cases requiring both calcium and magnesium supplementation for a positive response. Another study had suggested that dietary sulfur content was a primary determinant of milk fever incidence.[42] More recently, dietary potassium and sodium rather than calcium content has been implicated as a primary inducer of milk fever.[43] High dietary potassium not only interferes with magnesium availability, but contributes to metabolic alkalosis which hinders target organ response to the calcium homeostatic system.[41,43] Dietary cation anion difference (DCAD) as it relates to metabolic acidity or alkalinity has been a more recent area of active milk fever research relative to inciting factors and possible prevention.[41,44-46]

In spite of a tremendous increase in our knowledge about calcium homeostasis, we have not made tremendous gains in minimizing incidence of milk fever in aged dairy cows. Beyond the initial attempts at reducing calcium and phosphorus intakes to various modes of supplementing vitamin D metabolites or their analogs; manipulating prepartum DCAD shows the greatest promise for a practical method of milk fever prevention.[47,48] Forage analyses from all areas of the country have shown that forage potassium content is rising. This places a serious strain on magnesium status and DCAD in many prepartum diets, leading to increased milk fever problems in a herd. This is a critical issue to be addressed by the practitioner.

Although anionic salt programs are seen as a practical method of dealing with milk fever problems using available feed ingredients; they do not come without risk. Most anionic salts are unpalatable and their use generally results in reduced DMI during this critical period just prior to calving. Other issues include costs; safe time frame for feeding; and required dietary calcium, phosphorus and magnesium content for appropriate clinical response. Problems associated with attempted anionic salt programs stem mostly from use of partial anionic salt programs and inaccurate assessment of DCAD as a result of incomplete forage analysis data. Many herd "outbreaks" of milk fever can be directed back to a change in forage without consideration to changes in macromineral content and its effect on DCAD. Practitioners can provide a tremendous service to their dairy clients by routine monitoring of dry cow forages and diet for changes in macromineral content and subsequent alterations in DCAD. If not using anionic salt programs, similar monitoring would be critical to maintaining moderate calcium and phosphorus intake and appropriate magnesium content relative to dietary potassium concentration.

Microminerals and Vitamins

Although microminerals and fat-soluble vitamins are not directly associated with periparturient metabolic disease problems, they do play a role in transition cow and neonate performance. Trace minerals are lost during gestation to the fetus where they are concentrated in the liver to be used as a postnatal mineral reserve.[49-52] Fetal hepatic micromineral reserves are also augmented by consumption of colostrum, a highly concentrated source of most essential nutrients. Therefore, available neonatal nutrient reserves are the sum of placental transport and colostrum consumption, both of which are highly influenced by maternal nutrient status. In contrast to the microminerals, fat-soluble vitamins like vitamins A and E do not appreciably cross the placenta resulting in no gestational liver reserve.[19,53] The neonate's primary source of vitamins A and E comes via colostrum ingestion supplied from an adequately supplemented dam.[19,54] Nutrient concentrating ability of the fetal liver can only partially compensate for maternal nutrient deficiencies. A greater decline in nursing beef calf's selenium (Se) status was observed in calves from Se-deficient compared to Se-adequate dams.[55] Adequacy of neonatal nutrient reserves might explain differences in time frame and severity of specific nutrient deficiency disease occurrence.

From the dam's perspective, gestational micromineral and vitamin losses may significantly affect her reserves and their metabolic function. All too often mineral and vitamin supplementation is reduced or interrupted during the dry period. Deficiencies of microminerals and fat-soluble vitamins have been related to retained placenta and compromised immune function problems.[19,56,57] A compromised immune system may lead to increased incidence of metritis, mastitis or other infectious disease process. In short, it is absolutely essential that the pregnant cow receive an adequate amount of all minerals to support both maternal maintenance and conceptus development throughout the duration of gestation to minimize deficiency disease problems of either the dam or neonate.

Assessing Nutritional Status

Veterinarians, producers and nutrition consultants alike seem to be interested in extracting pertinent information relative to herd nutrition and health status from simple blood tests. Metabolic profiles, defined as a series of specific analytical tests run in combination, are commonly used in all veterinary hospitals as an aid in diagnosis of individual animal health problems. Application of this diagnostic procedure on a herd basis has been questioned relative to its validity and sensitivity in defining a problem as well as its cost. Unfortunately in many herd situations, blood analyses are used preferentially in lieu of other more appropriate diagnostic procedures such as ration evaluation and physical exams and without regard for proper technique to ensure sound diagnostic information. However, blood metabolite analysis can reveal some useful information if properly interpreted in conjunction with animal and ration evaluations.

Animal Selection

The goal of any metabolite profiling is to obtain the "population" mean and determine dynamic changes over differing physiologic states. To obtain this we need to sample large numbers of animals. Initially, cost is the main deterrent to large animal numbers; however, why not pool samples since we are interested in mean value and not individuals? Samples can be pooled by appropriate physiologic states to allow interpretation

of dynamic changes in "population" means over a period of time. For example to address a fresh cow problem, it is suggested that pooled samples be collected from recently dry cows (>7 days following dry-off), close-up dry cows (<2-3 weeks prior to calving) and fresh cows (< 30 or < 60 DIM). Other appropriate sample pools can be determined given the specific problem to be addressed. By pooling samples you are obtaining information from a greater number of animals for much less cost. Rather than the standard 21 samples to calculate 3 group means, you may submit 3 pooled samples which represents a mean of 10 to 20 animals each. The only negative part to this variation is the loss of statistical evaluation, i.e., population variance. However, this is not a major limitation. Proper identification of appropriate animal groups or pools is absolutely critical if one is to obtain useful data.

For data from these pooled samples to be relevant, all cows should be equally represented. It is preferred to have samples drawn only from nonclinical animals to more accurately represent the population. If needed, you could pool both clinical and nonclinical animals within a given group for comparison. To be able to appropriately interpret changes from one physiologic state to another at a single point in time, all animals should have been exposed to the same diets and management environments. This means to say that the fresh cows sampled today received the "same" diet that the early dry cows are currently receiving. If a dietary change was made recently, then comparisons between physiologic states are not appropriate. If no changes were made, then compare dynamic changes in "population" means for specific metabolites in accordance with clinical signs and ration evaluation.

Sample Collection

Sample collection and handling are important if one is to expect useful diagnostic information in return. Blood samples should be taken from either jugular or coccygeal veins with a minimal amount of stress. Blood samples from mammary veins are not appropriate given the loss of nutrients into the mammary gland. Lower concentrations of phosphorus and potassium have been documented in jugular compared to coccygeal blood samples as a result of salivary gland uptake.[58,59] Time of sampling relative to feeding and feeding management may also influence metabolite concentrations and should be considered in the decision process of when to sample. If herds are being repeatedly sampled as a monitoring tool, samples should be taken at approximately the same time of day to minimize diurnal and prandial variation.

Vacuum tubes are the most common and easiest form of sample collection. A variety of vacuum tubes are available. Vacuum tubes are colored coded for specific diagnostic test procedures based on the specific anticoagulant or additive present in the tube (Table 4). Most commonly a single serum sample is collected; however, in some cases a whole blood sample may be desired. Extreme efforts should be taken to prevent hemolysis of the sample. All samples should be properly identified with animal and group id and date of collection. Other pertinent information for interpretation of the metabolic profile would include: animal age, lactation number, milk production level, milk composition, days in milk, pregnancy status and body condition score.

Table 4. Description of blood collection tubes used for metabolic profiles.

Stopper Color	Additive	Sample Obtained	Intended Use/Disadvantages
Red	None	Serum	Routine use for all tests./ Prolonged clot exposure results in ↓ glucose, Ca and ↑ phosphorus. Hemolysis problems in poorly handled samples.
Gray	Na Fluoride or K Oxalate	Serum	Glycolytic Inhibitor for sensitive glucose analysis
Royal Blue	plastic stopper ± Na Heparin	Serum or Plasma	Trace mineral analysis
Lavender	EDTA	Whole Blood Plasma	Routine use for Complete Blood Count / EDTA chelates Ca, Mg and ↓ enzyme activities
Green	Na Heparin	Plasma Whole Blood	Routine analyses for either plasma or whole blood / No effect on metabolites

Analytical Tests

As for metabolite assays, the author routinely runs a complete profile as defined by the Clinical Pathology Laboratory, College of Veterinary Medicine, Oregon State University which includes: blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, total bilirubin, alkaline phosphatase (ALP), creatine kinase (Ck), γ-glutamyltransferase (GGT), aspartate aminotransferase (AST), sodium (Na), potassium (K), chloride (Cl), calcium (Ca), inorganic phosphorus (P) and magnesium (Mg). In addition, total cholesterol and nonesterified fatty acids (NEFA) are determined. All these tests only require serum although they can also be run on plasma from a green stopper tube. Assessment is based on absolute values compared to reference ranges and differences between defined groups specifically related to energy balance (NEFA values and BCS changes), protein status (BUN, Creatinine, Total protein, Albumin, Ck), macromineral status (K, Ca, P, Mg) and liver function (cholesterol, GGT, AST, Bilirubin).

Interpretation of Results

Interpretation of metabolic profiles requires some standard, laboratory-dependent reference values for comparison. These reference values should represent a population mean and variation from a defined population of animals clinically evaluated to be free of disease and other health problems. The reference range represents the population mean ± 2 standard deviations. Each population mean needs to be statistically analyzed for a normal distribution. Median values should be used in

place of means for metabolites not showing a normal distribution. A question needs to be posed at this point in time. Since it has been shown that stage of lactation has significant effects on blood metabolite concentrations, should reference values be established accordingly? At present this has not been done. Research is currently underway to ascertain if periparturient metabolite concentrations are significantly different from currently established reference values.

Pooled mean metabolite values are compared to reference values to assess differences. As a general rule, means of pooled samples should be near the midpoint of the reference range. At this point, there is need for some intuitive interpretation. For example, if Ca concentration for fresh cows is 9 mg/dL and the reference range is 9 to 12 mg/dL, this might be interpreted to suggest a potential problem with subclinical hypocalcemia. The measured mean of 9 mg/dL represents a population with approximately 50% of the individual values above and below. This suggests that a number ofindividuals would have serum Ca concentrations below the normal range. Of course interpretation ofmetabolic profile results has to be considered in light of presenting problems in the herd. If the herd is experiencing clinical signs consistent with subclinical hypocalcemia, e.g., slow increase in feed intake and milk production, displaced abomasum and ketosis problems, this would be supportive evidence of the metabolic profile results. Without population variance determinations, you can not really determine how significant mean differences are. Yet, with many metabolites, like BUN, Ca, Mg or glucose, you can eliminate the possibility that a single sample was sufficiently low or high to skew the mean. For low BUN values, it is difficult to have values approaching zero whereas for other metabolites, if the sampled cow had an extremely skewed value, it would have been exhibiting clinical signs and would not have been sampled. This also reinforces the issue of having more animals per pooled sample.

Energy Balance

Energy balance is by and far one of the most critical nutritional factors impacting on animal health, lactation and reproductive performance. Traditionally we have monitored changes in energy balance via body weight and condition changes over time. This procedure, however, may not be a sensitive enough tool when dealing with the transition cow. There is no doubt of a functional role for assessing body condition score changes with lactational performance. Another parameter which might be useful is ketone body concentrations. At present measurement of ß-hydroxybutyrate (BOHB) concentrations is commonly used. However, BOHB concentrations may not be sensitive enough and can come from other dietary sources. Measurement of blood acetoacetate concentrations would be preferred; however, this is not a feasible test for routine field usage as a result of rapid deterioration of acetoacetate. A traditional research procedure has recently received much interest in the clinical field. This is measurement of nonesterified fatty acids (NEFA) as a determination of energy balance. Many research studies have shown good correlations between energy balance and serum NEFA concentrations. Serum NEFA concentration is the result of adipose tissue catabolism of triglycerides and there is no other dietary source. Circulating NEFAs are then absorbed by the liver and other tissues for metabolism to energy. Concentration of NEFA then directly reflects the amount of adipose tissue catabolism taking place. The basis for NEFA and cholesterol recommendations come from studies and observations associating higher NEFA and lower cholesterol concentrations in cows with higher incidence of periparturient metabolic disease.[15,16] Total cholesterol and NEFA reference values are based on data from Michigan State University Clinical Nutrition Laboratory (Table 5). In the author's experience, serum NEFA concentrations seem to be more sensitive to energy balance changes than body condition scoring in transition cow situations.

Protein Evaluation

Assessing protein status is a bit more difficult than energy balance. At present there is no single metabolite which can be measured which directly reflects protein status. As a result, a combination of metabolite parameters need to be utilized, including BUN, creatinine, total protein, albumin and Ck. Urea nitrogen concentrations are influenced by a wide variety of interrelated parameters including: dietary protein intake and rumen degradability; dietary amino acid composition; protein intake relative to requirement; liver and kidney function; muscle tissue breakdown; and dietary carbohydrate amount and rumen degradability. Creatinine is used to assess renal function and its impact on BUN values. Total protein and albumin reflect availability of protein and their concentrations decline in the face of protein deficiency. However, this occurs over a period of time. Albumin has a fairly short half-life and can reflect protein deficiency problems over a period of a month or two. Creatine kinase is released from muscle when it is catabolized or injured. In most dietary protein deficiency

Table 5. Suggested serum values for total cholesterol and nonesterified fatty acids (NEFA) in the periparturient dairy cow.

Serum Metabolite	Early Dry	Close-up Dry	Fresh Cow
Total Cholesterol, mg/dL	> 80	> 75	> 100
NEFA, mEq/L	< 0.325	< 0.40	< 0.8

[1]Michigan State University Clinical Nutrition Laboratory, Dr. T. Herdt, personal communication.

situations, BUN values will be low (<10 mg/dL) with normal albumin concentration (>3.5 gm/dL) in the early dry cows. Close-up dry cows will have low to moderate BUN, lower albumin and elevated Ck values. Fresh cows generally have low BUN and low albumin (<2.5 gm/dL). These fresh cows seemingly fail to properly respond to any disease insult. Cows die from metritis, mastitis, foot rot and anything else without antibiotic therapy. An interpretation of this situation is that there are no amino acids available to support the immune system and it fails, predisposing the animal to any bug which comes along.

In other situations related to dietary protein deficiency, a high prevalence of retained placentas, metritis, ketosis and eventually displaced abomasum can be seen in the fresh cows. This may be associated with interrelated issues of energy balance and liver function. Recent research work with prepartum protein supplementation has suggested improved energy balance status and liver function.[15,31,32] These results may relate back to the critical role of amino acids in fetal nutrition and the physiologic processes in place to ensure adequate fetal nutrient supply at the expense of the dam.

Mineral and Vitamin Status

Nutrients which are homoeostatically regulated, i.e., calcium, sodium, glucose and to some extent phosphorus and potassium, will not show dramatic changes in their blood concentrations over a wide range of dietary situations. This then makes them poor indicators of metabolic status, unless the homeostatic mechanism is deranged. Sampling cows at points in time where they are metabolically stressed, i.e., just prior to and following calving, could potentially result in identifying cows which are more prone to metabolic disease problems. For trace minerals, whole blood or serum concentrations are buffered from acute changes as a result of dietary problems through mobilization of storage mineral, usually from the liver. This suggests that liver trace mineral status may be a better indicator of dietary adequacy, whereas measurement of mineral-specific enzyme activity better reflects the presence of overt clinical deficiency disease compared to blood concentrations. Many trace mineral concentrations in blood are influenced by disease. Bacterial infections induce sequestering of iron and zinc and elevation of copper. This could certainly confound interpretation of blood mineral status. Fat-soluble vitamins can be easily assessed via serum or liver concentrations. Again, liver concentrations would reflect a storage pool. Diurnal and periparturient changes in serum vitamin concentrations have been documented and need to be accounted for in any interpretation.[19,56]

Summary

As many dairy practitioners and producers have already come to know; how well a cow fares through the transition period will make or break the entire lactation. Although periparturient diseases primarily occur during lactation, they truly are initiated during the late gestation period. Data supporting this phenomenon and documenting the metabolic adaptations necessary to support lactation have been described. In order for a cow to adequately supply nutrients to support pregnancy and subsequently lactation, she needs to metabolically adjust to increase glucose and amino acid availability to reproductive tissues and acclimate maternal nonreproductive tissues to alternative nutrientsources. If this metabolic adaptation is exaggerated as a result of inadequate maternal nutrition, metabolic disease could result. The critical role of amino acids as both a fetal nutrient and a primary source of maternal gluconeogenic precursors may be a key piece to the periparturient disease puzzle. Ensuring continuous adequate delivery of nutrients throughout the dry period is a critical controlling factor in preventing periparturient disease problems. One must be diligent in identifying and addressing factors that initiate declines in DMI. Routine assessment of dietary nutrient content and its impact on animal nutritional status should be a monitoring tool used to prevent transition cow problems. As we come to better understand the factors which affect metabolites, we can adjust and better assess nutritional status. Veterinarians can and should be primary initiators of such monitoring programs.

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