Pregnancy toxemia and metabolic changes of transition in small ruminants

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Abstract

The objective of the presentation is to reacquaint the practitioner to pregnancy toxemia of small ruminants, and provide an in-depth discussion of metabolic alterations that lead to and are diagnostic for the disease process. Pregnancy toxemia is one of the most common metabolic diseases of small ruminants. The gravid uterus consumes significant glucose in late pregnancy, especially with multiple fetuses, placing the dam in a state of energy imbalance. Subsequent fat mobilization initiates a cascade of events that may ultimately lead to deranged metabolism and clinical disease. Ensuring the diet can adequately provide sufficient energy and protein to support fetal development is the cornerstone of disease prevention. Addressing issues of dietary fiber content and dry matter intake are as important as energy or protein density. Monitoring of dietary composition and animal blood metabolites can be a part of the overall flock health program to prevent significant disease consequences.

Résumé

Cette présentation a pour but de raviver les connaissances des médecins vétérinaires sur la toxémie de gestation (ou toxémie puerpérale) chez les petits ruminants et de discuter en profondeur des altérations métaboliques qui mènent à la maladie et guident le diagnostic. La toxémie de gestation est l'une des maladies métaboliques les plus courantes chez les petits ruminants. L'utérus gravide consomme une quantité significative de glucose en fin de gestation, en particulier en cas de fœtus multiples, ce qui place la femelle en déséquilibre énergétique. Une mobilisation des matières grasses s'en suit, qui déclenche une cascade d'évènements pouvant mener à un dérèglement du métabolisme et à la maladie clinique. S'assurer que la ration alimentaire fournisse assez d'énergie et de protéines pour soutenir le développement du fœtus est la pierre angulaire de la prévention de cette maladie. De même, il est aussi important d'examiner la teneur en fibres de la ration et l'ingestion de matière sèche que l'énergie ou la densité des protéines contenues dans cette même ration. Ainsi, le suivi de la composition des rations et des métabolites sanguins des animaux peut faire partie d'un programme de santé globale d'un troupeau qui aidera à éviter la toxémie de gestation, une maladie aux conséquences significativement néfastes.

Introduction

Pregnancy toxemia (pregnancy ketosis or twin lamb/kid disease) is a metabolic disease of goats and sheep commonly occurring in the last six weeks of gestation, especially in dams with multiple fetuses.[26] A similar syndrome can occur in llamas and alpacas, even though they do not have multiple fetuses. Negative energy balance with associated mobilization of fatty acids (NEFA) from adipose stores is the underlying problem. Factors inducing a reduction in feed intake (pregnancy, poor-quality forages, feeding management) or increasing energy requirement (rapid fetal growth, lactation, environmental conditions) contribute to the duration and magnitude of negative energy balance and predisposition to aberrant metabolism, leading to subclinical or clinical disease. Addition of external stressors such as severe weather, sudden changes in feed, other disease or transportation further accentuate negative energy balance. Mortality rate is high in affected animals when liver function is compromised as a result of fatty infiltration.

The disease course varies, but generally develops over three to 10 days. A more acute onset is usually associated with a sudden stress or inefficient animal observation. Appetite is poor or absent, with decreased consumption of grain observed first. Dams separate from the herd, lag behind, and become depressed and gaunt. Clinical signs are those observed with involvement of the central nervous system. Chewing, teeth grinding or vigorous licking movements may be seen. Evidence of blindness develops, the animal runs into objects, shows little or no reaction when approached, and wanders aimlessly. Dullness and depression become progressively severe. There is reluctance to move. Eventually they become sternal or laterally recumbent, and show little or no response to their environment. The dam becomes comatose and eventually dies. The objective of this presentation is to describe critical maternal and fetal metabolic processes, and how nutritional management influences occurrence of pregnancy toxemia and how it can be used in prevention.

Metabolic Challenges of the Transition Period

An appreciation of the exquisite metabolic adaptation the doe or ewe must undergo to achieve a successful transition from pregnancy into lactation is key to understanding the critical role of nutrition on metabolic disease and reproductive performance. Minimal data are available regarding pregnant doe metabolism and nutrition. Given the similarity in metabolic responses observed with dairy cattle and sheep, current research concepts regarding physiologic alterations associated with the transition from pregnancy to lactation can be extrapolated from these species.

An exponential fetal growth pattern places the greatest nutritional burden of pregnancy on the late pregnant ewe and doe, with greater than 60% of fetal growth occurring in the final month of gestation.[14,24] Glucose is the primary nutrient required by both the mammary gland and gravid uterus for metabolism.[4] The mammary gland converts glucose to lactose, while the gravid uterus oxidizes glucose as its primary metabolic fuel. Most energy derived by the gravid uterus comes from the oxidation of glucose, lactate, and amino acids.[1,4] Other potential energy substrates for the ewe or doe 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.[1] Complete oxidation of glucose and lactate can only account for 60 to 70% of the total fetal caloric requirement.[2] This suggests amino acids account for 32 to 40% of the total conceptus caloric requirement, in addition to providing the necessary substrate to support substantial protein synthesis activity.[3,8]

In periods of maternal under-nutrition, the fetus has little flexibility in terms of available alternative metabolic fuels. Fetal glucose and acetate 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.[1,4] 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.[8] These data clearly demonstrate that amino acids are essential fetal energy substrates, especially during periods of maternal under-nutrition, and place an additional protein utilization burden on the dam.

In contrast, fatty acids and ketone bodies can contribute to energy for the mammary gland and milk fat production, but cannot provide precursors for lactose synthesis; hence, milk yield will be substantially reduced in the face of maternal glucose deficiency. Excessive fat mobilization and ketone production resulting from maternal negative energy balance will contribute to a greater risk of metabolic derangement, resulting in ketosis and hepatic lipidosis.

Maternal Nutrition Effects

Data from cattle and sheep suggest nutrition of the dam at all stages of gestation can influence neonate viability and productivity. In reviewing factors responsible for contributing to prepartum and partum lamb losses,[6,25] nutritional deficiencies and toxicities influenced all factors. Similar contributing factors can be reasonably assumed for goats. Fetal growth pattern is influenced by a variety of interrelated factors including fetal genotype and sex, maternal uterine environment, ambient environment, and breed of sire.[2] However, the primary determinant of fetal growth is the availability of nutrients from the dam.

Birth weight is the single most important factor determining postnatal survival. Extremely heavy birth weight is more associated with dystocia, while lighter birth weight kids, typical of twins and triplets, have higher mortality rates.[30] Dynamic in vivo measures of fetal sheep crown-to-rump length found fetal growth to be deterred or completely stopped during periods of induced maternal hypoglycemia during late pregnancy.[18] Twin-bearing ewes fed an 8% crude protein (CP) diet gave birth to lambs that were 20% lighter than lambs born to similar ewes fed isocaloric diets with either 11 or 15% CP.[15] In contrast, additional protein feeding (11.8% CP) to singleton-bearing ewes resulted in larger lambs (10.8 vs 9.5 lb; 4.9 vs 4.3 kg) with greater birthing difficulty and higher mortality rate, compared to ewes fed to requirement (8.7% CP).[22] Besides differing in using twin or singleton pregnant ewes, dietary treatments were initiated at 110 and 85 days of gestation for these two studies.

Maternal dietary influence on fetal growth is more complicated than simply addressing under- or overfeeding relative to requirement. Maternal body condition score and dietary nutrient status relative to period of fetal and placental growth are confounding variables.[5] Fat ewes partition more nutrients to the gravid uterus, maintaining fetal growth during periods of moderate under-nutrition in late pregnancy, compared to lean ewes.[17] Lean or moderately fat ewes fed ad libitum in late pregnancy had similar placental and fetal birth weights despite different intake amounts (29% higher for lean ewes), suggesting placental mitigation of available nutrients in controlling fetal growth.[16]

In primigravid, singleton-bearing ewes, placental growth and ultimately, lamb birth weight was restricted when fed for rapid growth after the first trimester.[31] Rapid maternal growth during the first trimester fol-

lowed by moderate growth stimulated compensatory placental growth and moderate-birth-weight lambs.[31] Placental weight is the primary determinant of fetal weight.[11] Fetal cotyledon number was influenced by first-trimester nutritional status, whereas cotyledon weight was mediated by second-trimester nutrition.[31] Fetal number and placement within uterine horns further mitigate the relationship between gestational nutrition and fetal growth.[11]

Beyond birth weight, maternal milk production will affect growth and survival of the neonate. Inadequate nutrition during late pregnancy influences milk production and composition,[28] possibly as a result of compromised mammary gland development.[7] Dietary protein content of 11% CP (9.8 g/kg $BW^{.75}$), slightly higher than National Research Council (NRC) recommendations, is recommended for adequate late-gestation nutrition of the doe to meet fetal and subsequent lactational needs.[27]

Nutrition to Prevent Periparturient Disease

These described changes in nutrient requirements over the transition period require appropriate modifications in the feeding program, as well as metabolic alterations by the dam to adequately support late gestation and lactation. If these metabolic changes are not effectively enacted, metabolic disease and reduced neonate viability may result. Four critical control points during the transition period that need to be addressed to prevent periparturient problems are: 1) maximizing dry matter intake; 2) minimizing negative energy and protein balance; 3) maintaining calcium homeostasis, and 4) minimizing immune system dysfunction.[10] These key control points were described for periparturient disease control in dairy cattle, but can be equally applied to small ruminants.

Optimizing Dry Matter Intake

Dietary recommendations for energy, crude protein, calcium, and phosphorus for the late-gestation ewe or doe are 1.5 to 2.0 times greater compared to early gestation, with an even larger increase to support lactation.[20] Of concern in reviewing dietary nutrient intakes recommended by NRC publications, one notices an expectation for dry matter intake to increase throughout these transitions. This is a point of concern in late pregnancy, where physical fill limitation and other metabolic or endocrine factors may decrease intake capacity, thus resulting in greater potential for pregnancy toxemia and hypocalcemia metabolic problems.[9]

Neutral detergent fiber (NDF) content of forages or total diet has been shown to be a primary mediator of intake in dairy cattle. Research in cattle and sheep has shown an optimal limit of NDF intake as 1.2% of body weight.[19] Other work has shown a lesser ability of pregnant cows to consume NDF. Expected NDF intakes for pregnant cows ranges from 0.8% of body weight at the end of pregnancy up to approximately 1.0% of body weight during the early dry period. Younger animals (first parity) have lower NDF capacity (0.1 to 0.2 units lower) compared to mature animals. Other issues such as forage quality and environmental factors will also influence intake capacity.[9] Role of forage quality on potential intake as determined by NDF intake capacity is demonstrated in Table 1. As forage (or total dietary) NDF increases, maximal intake capacity is reduced. For example, if forage (or total diet) NDF is 50% and NDF intake capacity is 1% of body weight, then the animal could consume 2% of body weight as forage or total diet. If NDF intake capacity is reduced to 0.8% of body weight, then intake would be only 1.6% of body weight for this same NDF level. The NRC recommendations assume an intake level between 1.8 and 2% of body weight for late pregnant cows, suggesting a maximal dietary NDF content less than 44%.

Limitation of intake by NDF physical fill can be applied to other ruminant species, including small ruminants.[9] However, selective feeding behaviors typical of goats may overcome dietary limitations from NDF content. This is assuming the animal is capable of separating digestible feed components from fibrous components. Legume forages facilitate this process, as stems are separate from the leaves; however, grass forages do not have this distinction. Data from the literature suggest sheep have similar NDF capacities during pregnancy as cattle.[15,23]

In the McNeil study, twin pregnant ewes were fed isocaloric diets with differing protein content (8, 11, and 15% crude protein).[15] Diets contained similar NDF content ranging from 39.3 to 42.9%. Calculated NDF

Table 1. Predicted dry matter intake (DMI) as a percent of body weight related to neutral detergent fiber (NDF) intake capacity.

Forage NDF %	DMI	NDF capacity (% of body weight)			
		1.2	1.0	0.8	0.6
38	Intake as a % of body weight	3.16	2.63	2.11	1.58
42		2.86	2.38	1.90	1.43
44		2.61	2.27	1.74	1.36
46		2.73	2.17	1.82	1.30
50		2.40	2.00	1.60	1.20
54		2.22	1.85	1.48	1.11
58		2.07	1.72	1.38	1.03
62		1.94	1.61	1.29	0.97
66		1.82	1.52	1.21	0.91

intake as a percent of body weight was 0.71, 0.78, and 0.89 for 8, 11, and 15% crude protein diets, respectively. These diets were fed between 110 and 140 days of gestation, and are consistent with observed lower NDF intake capacity of late-pregnant cows. Of interest is the dietary protein effect, which may be the result of improved fiber digestibility with increasing dietary protein. In another study monitoring intake with silage-based diets, calculated NDF intake as a percent of body weight decreased with increasing week of gestation and fetal numbers (Table 2).[23] Again, NDF intake was below 0.8% of body weight in late pregnancy, similar to what is observed in dairy cattle. In this same study, forage quality effects on NDF intake at different weeks of gestation and pregnancy status were evaluated. Again, higher fetal numbers and later gestational status resulted in lower NDF intake capacity.

Based on NRC recommendations, a late-pregnant ewe (154 lb or 70 kg body weight) with twins should consume 4.0 lb (1.8 kg) dry matter (2.6% of body weight).[20] Using a NDF intake capacity of 0.7% of body weight, maximal dietary NDF content would be 27% (0.7/2.6*100). Extending this example further, if one assumes the 65% forage ration suggested by NRC, this would mean forage NDF could not exceed 41%. Forage quality may be the most limiting factor in maintaining transition intake for small ruminants. To maintain high intake potential, late-pregnant animals should receive higher quality forages (<40% NDF), have feed available at least 21 hours per day, and should be managed to minimize excess body condition.

Table 2. Calculated neutral detergent intake (NDF) as a percent of body weight in ewes fed differing quality silages over weeks of gestation and pregnancy status.[a]

Pregnancy week[b]		NDF intake as % of body weight		
		Singles	Twins	Triplets
15		0.83	0.81	0.74
16		0.81	0.73	0.71
17		0.81	0.65	0.68
18		0.74	0.65	0.64
19		0.69	0.62	0.59
20		0.70	0.60	0.55
Mean		0.76	0.68	0.65
Forage NDF%	Week	NDF intake as %BW		
		Singles	Twins	Triplets
48.5	15-17	0.82	0.74	0.71
63.8	15-17	0.78	0.70	0.70
44.9	18-20	0.83	0.70	0.70
48.5	18-20	0.71	0.62	0.59

[a]Adapted from Orr *et al*, *Animal Production* 1983;36:21-27.
[b]Silage (48.5% NDF) fed at 25% of dietary dry matter

Minimizing Negative Energy and Protein Balance

Nutrient balance is a function of dry matter intake and nutrient composition. If dry matter intake declines in late gestation, appropriate modifications to nutrient density will be necessary to ensure adequate nutrient intake. Otherwise, the pregnant dam will experience negative energy balance, which could lead to rapid mobilization of fat reserves and subsequent hepatic lipidosis and pregnancy toxemia. Increasing grain in the diet (0.75-1.5 lb; 0.34-0.68 kg/day) can help compensate for low dietary energy availability, as well as acclimate rumen microbes in an effort to prevent potential acidosis and off-feed problems.

Gestation diet protein content needs to be considered when grain is increased to accommodate intake. Maternal protein deficiency in late gestation seemingly has a greater impact on birth weight than does energy deficiency. Severe or prolonged maternal protein undernutrition can result in intrauterine growth retardation of the fetus, as well as negatively impact viability through decreased thermogenic capacity and reduced production of quality colostrum. Although the NRC recommends 10.3% CP diet for late-gestation ewes, this assumes an intake level of 2.6% of body weight.[20] Based on NRC nutrient amount recommendations and varying late gestation intake capacity between 1.8 and 2.4% of body weight, necessary dietary nutrient densities were calculated for twin pregnant ewes (Table 3). Ewes need to consume a 15% CP diet in order to equal daily protein needs as a result of reduced intake, consistent with the observations of the McNeil study.[15] If the diet cannot meet protein needs, then the dam will mobilize body protein to meet fetal amino acid needs. 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 a severe detrimental impact on health, lactation, and reproductive performance following parturition since these nutrient pools are critical to support early lactational nutrient losses.

Maintaining Calcium Homeostasis

Ewes and does can experience prepartum hypocalcemia as a result of insufficient calcium intake to meet fetal calcium demands. In addition, dairy breed does may experience postparturient hypocalcemia similar to the

Table 3. Impact of dry matter intake capacity on dietary nutrient content. Requirements based on 154 lb mature ewe in late pregnancy with an expected lambing rate of 180-225% (based on NRC, 2007 recommendations).[a]

NRC req.	DMI		ME	CP	Ca	P
Total	4.03 lb		4.37 Mcal	192 g	8.8 g	5.3 g
Density	2.6 % BW		1.08 Mcal/lb	10.3%	0.48 %	0.29 %
Adjusted intake level	lb	% BW	Mcal/lb	% DM	% DM	% DM
	2.8	1.8	1.56	15.1	0.69	0.42
	3.1	2.0	1.41	13.6	0.63	0.38
	3.4	2.2	1.29	12.4	0.57	0.34
	3.7	2.4	1.18	11.4	0.52	0.32

[a]Abbreviations: Req.= requirements; DMI = dry matter intake; ME = metabolizable energy; CP = crude protein; Ca = calcium; P = phosphorus; BW = body weight; DM = dry matter.

syndrome seen in dairy cattle. Pathogenesis of prepartum milk fever is uncertain, whereas cationic diets are primarily responsible for the postparturient syndrome. A primary initiator of hypocalcemia in small ruminants is inadequate dietary calcium to meet needs for fetal bone development and inappropriate dietary calcium-to-phosphorus ratio. Excess phosphorus in the diet can inhibit dietary calcium uptake and potentially suppress parathormone (PTH) activity that promotes vitamin D activation and increased efficiency of intestinal calcium absorption. Milk fever can be prevented by ensuring sufficient calcium and phosphorus are available in the diet, accounting for observed level of intake.

Minimizing Immune System Dysfunction

Trace minerals are lost during gestation from the dam to the fetus, where they are concentrated in the fetal liver to be used as a postnatal mineral reserve.[13] 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. The loss of mineral to the developing fetus from maternal circulation may compromise the dam's immune status by significantly reducing readily available mineral in support of immune responses. The degree to which the fetus was able to accumulate hepatic mineral reserves will impact growth, metabolism, and immune response in postnatal life. Hepatic mineral concentrations decline over the first three months of life, down to typical adult concentrations (dry weight comparison). If insufficient mineral was transferred during gestation, postnatal reserves will be insufficient to maintain postnatal needs, resulting in varying degrees of deficiency and impaired immune response.

In contrast to the microminerals, fat-soluble vitamins like vitamins A and E do not appreciably cross the placenta, resulting in minimal gestational liver reserve.[12,21,29] The neonate's primary source of vitamins A, D, and E comes via colostrum ingestion supplied from an adequately supplemented dam. These trace nutrients not only are required for normal growth and development of the lamb, but also are essential to normal function of the immune system. The loss of trace minerals and fat-soluble vitamins in late gestation may compromise the dam's immune status if she was in a marginal nutritional state. One should ensure that adequate supplementation of minerals and vitamins is available throughout the late pregnancy period. Free-choice mineral feeding is often the most economic and practical, but also opens the door for the greatest variability in potential intake, leading in many instances to marginal deficiencies.

Conclusions

Similar to transition cow feeding and management practices currently being employed on most dairy farms, transition programs for small ruminants can also be of use. Whether servicing camelid, sheep or goat enterprises, transition nutrition can have tremendous impact on animal performance and viability of the neonatal animal. Late-gestation diets should be formulated to at least meet the minimum NRC requirements, but adjusted to an appropriate intake level and forage quality. Based on current NRC nutrient recommendations, late-gestation diets for sheep and goats should contain between 13 and 15% crude protein and be fortified with minerals and vitamins. Good quality forage (<42% NDF) with 1.0 to 1.5 lb (0.45 to 0.68 kg) of a concentrate should be an adequate blend to meet energy needs of the animal. Veterinarians can play an important role in their client's transition program through nutritional monitoring of body condition score, forage quality, and metabolic parameters of energy balance and protein status.

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