Pregnancy toxemia in small ruminants: a review
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Abstract
Pregnancy toxemia is a metabolic disease of ewes and does with multiple fetuses in late gestation. While pregnancy toxemia has been well described in the literature for decades, a thorough understanding of the pathogenesis, individual predisposing factors, and treatment options still remains limited. Recent research has contributed to our understanding of the pathogenesis of this disorder and developing an improved diagnostic approach. In particular, an understanding of insulin regulation and development of insulin resistance, along with identification of markers of oxidative stress, has generated additional information in understanding individual animal variation for predisposition to development of the disease. The objective of this review is to present the current understanding of pregnancy toxemia including pathogenesis, various predisposing factors, clinical signs, available diagnostics, available treatment options, and discuss the current and future research which may result in an increased understanding of the disease, improved diagnostic efficiency, and provide better flock or herd management for prevention.

Keywords: Small ruminants, metabolic, insulin, pregnancy, diagnosis

Introduction
Pregnancy toxemia, also referred to as pregnancy ketosis, pregnancy disease, twinning disease, and fatty liver syndrome, occurs in all countries worldwide. It is most commonly found in multiparous ewes or does carrying multiple fetuses. The disease occurs more frequently in ewes than in does. The condition is generally brought on by a competition between the dam and her fetuses for glucose. Pregnancy toxemia is a metabolic disease that affects pregnant ewes and does during the last third of gestation, especially the last four to six weeks. This is the period of rapid fetal growth. Susceptibility is widely variable, with some individuals being more predisposed than others.

Small ruminants are an important income source in numerous countries and are gaining popularity in the United States. Economic losses associated with pregnancy toxemia could have lasting effects, especially in countries were nutritional support is limited. Increased industry drive for higher prolificacy combined with increasing feed costs and decreasing profit margins can also result in development of pregnancy toxemia within a given flock or herd.

The objective of this review is to present the current understanding of pregnancy toxemia including pathogenesis, various predisposing factors, clinical signs, available diagnostics, and available treatment options, as well as discuss the current and future research which may result in an increased understanding of the disease, improved diagnostic efficiency, and provide better flock or herd management for prevention.

Pathogenesis
Pregnancy toxemia is a complex metabolic disorder, and the full etiopathogenesis is not completely understood. Pregnancy toxemia is a severe form of ketosis, characterized by low serum glucose concentrations and high ketone body concentrations. Individual variation appears to be related to hepatic metabolic efficiency and ability to maintain functional insulin concentrations and maternal tissue responses, with some breeds (mainly those consistently delivering two or three offspring per litter) more predisposed to the condition. However, some highly prolific breeds, such as Finnish Landrace and Booroola Merino sheep, do not experience an increased incidence of pregnancy toxemia.

Maintenance of adequate concentrations of serum glucose is critical to brain function, fetal growth, and milk production. In ruminants, limited dietary glucose is absorbed because the ruminal flora is proficient at fermenting glucose. The majority of ruminant energy is derived from short-chain fatty acids including acetate, propionate, and butyrate, which are produced by the ruminal flora. Propionate...
is the most important glucose precursor in ruminant gluconeogenesis and derives from ruminal fermentation of high-carbohydrate-content feed. Ruminal fermentation of forage produces acetate, which is the precursor of long-chain fatty acids for fat storage. Serum glucose concentrations are largely maintained by gluconeogenesis, 85% of which occurs in the liver. Excess glucose is stored in the liver as glycogen but these stores are inadequate to supply the dam’s needs in late gestation. There is an increased sensitivity to hypoglycemic stress, such as prolonged feeding intervals, in ewes and does with multiple fetuses in late gestation. Hypoglycemia in these animals results from a reduction in the glucose production rate.

In late pregnancy ewes and does with multiple fetuses may become unable to maintain glucose homeostasis, resulting in a state of negative energy balance. This metabolic state results in a decreased ratio of insulin to glucagon and insulin resistance may result. It has been demonstrated that insulin plasma concentrations are reduced in ewes carrying more than three fetuses. The ability to maintain functional insulin concentrations and maternal tissue responses appears to be key to an appropriate metabolic adaptation to a negative energy balance where pregnancy toxemia does not develop. In a state of negative energy balance, glucogenic precursors from the diet or endogenous sources are not able to meet the total energy requirements, and the body shifts to other sources for energy maintenance during late gestation.

Fat mobilization is initiated in an attempt to compensate according to the degree of the negative energy balance. Lipases are activated that convert tissue fat into fatty acids and glycerol. The glycerol can then be converted into glucose in the liver, through hepatocyte mitochondria. Non-esterified fatty acids (NEFAs) are the major component of triglycerides (fat stored in the body) and are either used for production of energy via the Krebs cycle or are converted into ketone bodies (acetone, acetoacetate, and β-hydroxybutyrate [BHB]). The excessive release of NEFAs may overwhelm the liver’s capacity, in turn generating large quantities of ketone bodies, resulting in fat infiltration of the hepatocytes. Furthermore, the direction of NEFA metabolism is dependent on availability of oxaloacetate. Oxaloacetate, a substrate for gluconeogenesis in states of negative energy balance, is an intermediate in the Krebs cycle. If supplies of oxaloacetate are low, ketone formation results.

Acetoacetate, a ketone body, has been reported to generate superoxide radicals that form hydroxyl radicals. These free radicals exert a cytotoxic effect resulting in the accumulation of the final products of lipid peroxidation, such as thiobarbituric acid reactive substances (TBARS). These products can cause alterations in biomembrane permeability and lipid organization, as well as cellular dysfunction and membrane damage, ultimately leading to cellular death. Markers of oxidative stress have been demonstrated to be elevated in cows with subclinical ketosis. Al-Qudah et al. examined the role of hyperketonemia in initiating lipid peroxidation and evaluated the status of enzymatic and non-enzymatic antioxidant defense systems in ewes affected by pregnancy toxemia. An increased plasma concentration of TBARS suggested a significant increase in lipid peroxidation in ewes with pregnancy toxemia compared with healthy pregnant and healthy non-pregnant ewes. A decrease in antioxidant enzyme activity was also observed and may be associated with an imbalance between lipid peroxidation and antioxidant capacity in pregnant ewes. In that study, oxidative stress was determined to be caused by four factors: negative energy balance and ketone formation, increased free radical production resulting from increased metabolic activity during pregnancy, reduction of antioxidant reserve during pregnancy, and physiological adaptation of pregnant animals to lactation.
Predisposing factors

In the last four to six weeks of gestation, the ewe or doe experiences the most rapid fetal growth and demands from the pregnancy, while at the same time experiencing a decline in nutritional intake, predisposing the ewe or doe to a ketosis-prone metabolic state.\textsuperscript{2,7,19,20} In well-managed flocks or herds, individual variation may result in sporadic occurrence and low morbidity (<3%) that may be linked to genetic variation.\textsuperscript{4} In contrast, flocks or herds with improper nutritional management could experience outbreaks with morbidity rates exceeding 10% of the ewes or does.\textsuperscript{7} Mortality rates of affected animals can exceed 80%, especially if treatment is delayed.\textsuperscript{4}

Pregnancy toxemia can be classified into two general categories: primary and secondary. Primary pregnancy toxemia results from a combination of poor nutrition and a sharp increase in energy needs during late gestation, and most commonly affects older animals.\textsuperscript{2,7,20} It can be precipitated by other management or environmental factors. Factors that might predispose a ewe or doe to development of pregnancy toxemia include lack of feed availability, decreased feed quality, sudden feed changes, transportation during late pregnancy, shearing, vaccinating, and heat or cold stress.\textsuperscript{2,7,19} These factors, either singly or in combination, result in decreased feed intake, development of a negative energy balance, and result in the progression to a ketotic state.\textsuperscript{7} Decreased feed intake, even if only temporarily, can be detrimental because there is already limited abdominal space as a result of increased fetal size, and thus protracted limited feed intake\textsuperscript{6} Multiparous, thin ewes in their last trimester are at increased risk. Over-conditioned animals (body condition score >4/5) are at an elevated risk of pregnancy toxemia due to increased fat storage for mobilization to the liver,\textsuperscript{7} along with reduced abdominal space as a result of increased intra-abdominal adipose tissue.\textsuperscript{6} Secondary pregnancy toxemia is a result of conditions that cause reduced feed intake and increased energy needs. Concurrent disease, such as acidosis, water deprivation, hypocalcemia, infectious pododermatitis, pneumonia, heavy parasite infestation, vaginal prolapse, or chronic wasting diseases can result in development of secondary pregnancy toxemia.\textsuperscript{2,5,19}

While it has long been demonstrated that a lack of energy supply is responsible for the development of pregnancy toxemia, it is not likely to be the only major factor. Considering that pregnancy toxemia develops during late gestation and not during lactation when the energy demands are the highest, and that there are known breed-dependent differences, insufficient energy utilization rather than a complete lack of energy supply may be a contributing factor.\textsuperscript{21}

It is suspected that marked metabolic changes in late pregnancy may be the result of modified hormonal responses.\textsuperscript{22} Harmeyer et al. experimentally induced ketosis in Texel and German Blackface ewes that were over three years of age during different reproductive stages (late gestation, early lactation, and non-pregnancy/non-lactation) to measure the turnover rate of ketone bodies during hyperketonemia in a steady state condition.\textsuperscript{22} β-hydroxybutyrate concentrations in the blood were elevated through a continuous IV infusion of DL-β-hydroxybutyrate (D-BHB) to maintain levels similar to concentration usually present in ewes with clinical signs of pregnancy toxemia.\textsuperscript{22} Significant differences existed in maximal D-BHB turnover between reproductive states, with limited turnover observed during late gestation. The indication that ewes in late gestation, especially those carrying twins, have reduced utility of ketone bodies is surprising since these ewes undoubtedly rely to a greater extent on ketone bodies to satisfy energy needs, especially compared to ewes that are not pregnant or lactating.\textsuperscript{22} Reduced disposal of BHB during late gestation along with an increased rate of hepatic ketogenesis promotes hyperketonemia, facilitating development of pregnancy toxemia. Theoretically, several hormonal and metabolic factors could be contributing to this factor, with one possible candidate being insulin.\textsuperscript{22}

In recent years, insulin resistance during late gestation has been evaluated as a potential predisposing factor to development of pregnancy toxemia.\textsuperscript{21} Insulin appears to be less responsive in ruminants than in monogastric species, however it is still important for glucose homeostasis and also has anti-lipolytic activity in adipocytes and depresses ketone body formation. In cases of pregnancy toxemia where hypo/hyperglycemia, lipemia, and hyperketonemia are common, insulin resistance may be a major predisposing factor.\textsuperscript{21}

Duehlmeier et al. evaluated metabolic adaptations to pregnancy and lactation in ewes.\textsuperscript{23} Ewes were separated into two groups (high and low risk). The high-risk group consisted of 4.5 to 6.5 year old
German Blackheaded Mutton ewes, a breed that has been recognized as being highly susceptible to pregnancy toxemia. The low risk group consisted of 2.5 year old Finnish Landrace ewes, a breed that has been recognized for high prolificacy and low incidence of pregnancy toxemia. Blood samples were evaluated for glucose, insulin, NEFAs, and BHB concentrations at differing times during gestation and following parturition. The study revealed that high-risk ewes had decreased insulin and glucose concentrations during late gestation in comparison to low-risk ewes and ewes during lactation. Non-esterified fatty acid and BHB concentrations were elevated during late gestation in comparison to low-risk ewes. In a follow-up study, the same parameters were evaluated after the administration of an intravenous glucose tolerance test (IVGTT) at differing times during gestation and following parturition. High-risk ewes exhibited a lower insulin response and reduced glucose elimination following each IVGTT. Increased lipolysis in late gestation was only observed in the high-risk ewes. β-hydroxybutyrate concentrations were only elevated in late gestation in the high-risk ewes compared to the low-risk ewes, and during late gestation the BHB concentrations did not decrease at all after IVGTTs in the high-risk ewes. It is suspected that termination of lipolysis relies on the inhibition of hormone-sensitive lipase (HSL) and activation of lipoprotein lipase (LPL) by insulin, which is secreted in response to glucose. It is also suspected that control of ketogenesis is regulated in part by insulin. Insulin resistance in both of these scenarios could result in dysfunction of these pathways as observed in this study.

Clinical signs, diagnosis, and postmortem findings
Clinical signs in ewes and does vary in severity and progression of the metabolic derangements. Initially the clinical signs associated with pregnancy toxemia are vague, with affected animals isolating themselves from the remainder of the flock or herd. Affected animals will appear listless and obtunded and when moved to food sources will stand with the other animals, but do not eat. With the progression of hypoglycemia and ketonemia, neurological clinical signs (head pressing, circling, muscle tremors) will become apparent within one to two days with the resultant development of hypoglycemic encephalopathy. They are often hyperesthetic to tactile or auditory stimuli and are difficult to restrain once caught. Ewes and does may appear blind (lack of a menace or "star-gazing" appearance), ataxic, or disoriented. Feed intake decreases further, perpetuating the cycle. The ewe or doe will develop tachypnea and dyspnea with continued progression of neurologic signs to recumbency. Once recumbent, there is often a lack of abdominal muscle tone and urine scalding can be observed on the abdomen and hind legs. Chewing, teeth grinding, excessive salivation, and excessive licking may also be observed. In the advanced stages, severe neurologic signs, potential convulsions, and coma can be observed, followed by death. In some instances there may be a transient improvement if fetal death occurs, however more profound depression generally follows. Death is usually the result of renal failure or toxemia following death of the fetuses. Renal failure is thought to be the result of systemic hypertension caused by ketoadidemia. The onset of hypertension in affected animals results in renal dysfunction due to a decreased glomerular filtration rate. Progression of clinical signs generally ranges from 12 hours to seven days, but most commonly occurs over three to four days.

Differential diagnoses should include hypocalcemia, polioencephalomalacia, listeriosis, impending abortion, copper toxicity, and ruminal acidosis. Diagnosis of pregnancy toxemia is generally based on history and clinical signs. Ketosis is generally diagnosed by identification of excessive ketone production in the urine. Dipsticks and ketone powder both use the nitroprusside test to semi-quantify acetoacetate concentrations. Serum or plasma BHB concentrations can also be predictive of pregnancy toxemia. Normal BHB concentrations are below 8 mg/dL, whereas in cases of moderate ketosis associated with subclinical disease BHB concentrations are >15 mg/dL. Clinical ketosis is generally associated with BHB levels in excess of 25 mg/dL. Several studies demonstrated that increased BHB concentrations were a sensitive indicator for the complex alteration of glucose and lipid metabolism in pregnancy toxemia.

Other laboratory findings that might indicate the presence of pregnancy toxemia include elevated NEFA levels (>0.4 mEq/L), hypoglycemia, and in some cases elevated liver enzymes and hypocholesterolemia. In recent studies, hypotriglyceridemia and hypocholesterolemia have been
observed in subclinical and clinical cases of pregnancy toxemia, when compared to control groups, and in association with increased fetal numbers.\textsuperscript{12,25} Hypoproteinemia (hypoalbuminemia and hypoglobulinemia) can be observed in clinical cases of pregnancy toxemia, and could potentially be attributed to hepatic and/or renal failure.\textsuperscript{25,26} In the clinical or later stages of pregnancy toxemia, hyperglycemia (often associated with fetal death), hypokalemia, hypocalcemia, elevated creatinine, and elevated blood urea nitrogen (BUN) may be evident.\textsuperscript{25,26} Decreased serum fructosamine represents a persistent hypoglycemia and could also be used as an indicator of early pregnancy toxemia. Fructosamine, a ketoamine compound formed when glucose reacts with amino groups on proteins, is related to the average glucose concentration over a period of several weeks.\textsuperscript{4}

Recently levels of the antioxidant ceruloplasmin were shown to be a good indicator of feed deficiency in late pregnancy in Chios ewes.\textsuperscript{18} Ceruloplasmin is an acute phase protein that functions as a copper transporter, but also acts as an intravascular antioxidant in response to tissue damage and inflammation.\textsuperscript{18} Results from the study indicated that mean serum ceruloplasmin levels were not significantly different between groups until day 148 of gestation. At day 148 of gestation, representative of the last week of gestation, a significant rise in ceruloplasmin was observed in the feed deficient group of ewes.\textsuperscript{18} It is important to recognize, however, that ceruloplasmin at that stage of gestation could have also be elevated due to other factors including elevations in cortisol, ACTH, and estradiol-17\textbeta, which have been demonstrated to cause elevations in ceruloplasmin in pregnant females in other species.\textsuperscript{18} It is therefore important to recognize that further research is needed to establish elevated ceruloplasmin levels as an indicator of feed deficiency in pregnant small ruminants and as a marker for severity of pregnancy toxemia in clinical cases.

Due to expense of treatment and lack of success, especially in advanced cases, recent studies have evaluated diagnostic tools, which can be used in the field. Many producers and veterinarians use urine ketone test strips for the diagnosis of ketoacidosis. In dairy cattle ketone strip accuracy is reportedly variable due to factors including the nature of handling, interval from testing to reading, environmental conditions, and pigmenturia.\textsuperscript{27} Additionally, urine collection may be difficult. Recently a point of care (POC) meter designed to measure blood glucose and BHB concentrations in humans was evaluated in ewes.\textsuperscript{28} Comparison of POC BHB concentrations with reference laboratory concentrations showed that 93% of POC BHB concentrations were within 20% of the reference laboratory concentrations. Results for blood glucose concentrations revealed that only 68% of POC glucose concentrations were within 20% of the reference laboratory concentrations. These results suggest that the POC meter is clinically acceptable for measuring blood BHB concentrations, but not glucose concentrations.\textsuperscript{28} In general the POC meter demonstrated low blood glucose concentrations in comparison to reference laboratory results, and could result in overtreatment with administration of glucose substrates to increase blood glucose concentrations unnecessarily.\textsuperscript{28} It was noted that the laboratory’s reference limits for adult sheep might not have been appropriate for pregnant ewes. Overall human-derived devices, such as the POC meter, could be beneficial in evaluating BHB concentrations, becoming a useful on-farm diagnostic tool for pregnancy toxemia.\textsuperscript{28} Also, considerations for usefulness on-farm would need to be made with respect to animal handling facilities and operator training to perform venipuncture.

On postmortem examination, the carcass is either emaciated or in good condition with large quantities of intra-abdominal and subcutaneous fat.\textsuperscript{6,15} There can be differing degrees of fatty liver infiltration, with the liver generally enlarged, pale and friable (Figure 1). On histological evaluation of liver samples obtained from ewes suffering from pregnancy toxemia, microvesicular steatosis with lipid droplet accumulation was reported (Figure 2).\textsuperscript{29} The presence of multiple fetuses is also observed grossly, and depending on when fetal death occurred, autolysis may be present.\textsuperscript{6,7,19} Other gross abnormalities that might be identified include enlarged, hemorrhagic adrenal glands.\textsuperscript{4} Renal and cerebral lesions are often not identified on gross examination, but might reveal changes on histological examination.\textsuperscript{6} Aqueous humor concentrations of BHB can correspond to antemortem serum concentrations and help diagnose the condition in the absence of significant lesions grossly.\textsuperscript{5}
Treatment, flock/herd management, prevention

Treatment and prognosis for recovery of pregnancy toxemia are highly dependent on the stage of the disease at time of diagnosis and initiation of treatment. Current treatment protocols are based on two general principles: administration of energy sources, and removal of factors that increase energy requirements of affected animals. Early intervention may be effective; however, in general, response to treatment is poor because the disease becomes irreversible in its later stages.

If the ewe or doe is in the early stages of the disease and is still responsive and willing to eat, dietary modification and supplementation with glucogenic precursors may be sufficient. Affected animals should be separated from the remainder of the flock or herd and provided adequate shelter. It is important to ensure that high quality forage be provided along with an increased energy source in the form of easily digested concentrates. In addition to dietary modification, glucogenic precursors may be orally administered. Oral glucogenic precursors include propylene glycol (60-200 mL PO q12 hr for 6 days) or glycerol (60 mL q12 hr for 3-6 days). Other sources such as calcium propionate, sodium propionate, liquid molasses, sodium lactate, or ammonium lactate may be used as glucose sources, but are not metabolized as quickly as propylene glycol. Oral administration of a concentrated dextrose and electrolyte solution may also be effective. There are a wide variety of commercially available products containing the above precursors that have been used clinically with varied results. Calf electrolytes for neonatal diarrhea (PO q12 hr for 1-2 days) can combat acidosis and dehydration.

If the ewe or doe is in a more advanced stage of the disease, more aggressive supportive therapy is necessary and the prognosis becomes more guarded. Generally in these cases, unless the animal has high reproductive value, treatment is not attempted due to cost limitations. The hypoglycemia should be corrected by oral and/or intravenous administration of a glucose solution, such as 5% dextrose. It is important to recognize that hyperglycemia can result in later stages of the disease, and glucose levels should be evaluated before initiation of treatment. In combination with glucose treatment, insulin therapy should be initiated and monitored closely. Insulin therapy facilitates tissue glucose uptake and inhibits fatty acid mobilization.

Acid-base status, degree of dehydration, associated electrolyte abnormalities, and renal function should be evaluated and appropriate treatment and fluid therapy provided in clinical cases of pregnancy toxemia. Fluids with electrolytes can be administered either orally or intravenously depending on the condition of the animal. Additional treatment modalities that might prove to be beneficial include administration of B-complex vitamins to stimulate the appetite and administration of flunixin meglumine. Offering a variety of feeds and fresh cut grass may also help to stimulate the appetite. In some situations commercially concentrated pellets can be soaked and administered as a gruel via a stomach tube to provide supportive enteral nutrition or transfaunation could be considered if a source of rumen fluid is available. Due to the potential correlation between ketonemia and oxidative stress in ewes with pregnancy toxemia, it may also be imperative to consider antioxidants as a useful addition to protocols for treatment (and potentially prevention) of pregnancy toxemia. In cases where high parasite loads are diagnosed, it is recommended to consider administration of a broad-spectrum anthelmintic for treatment of gastrointestinal nematodes and liver trematode parasites. It is important to consider the choice of anthelmintic when administering to a pregnant animal.

Recombinant bovine somatotropin has been administered experimentally to ewes with naturally occurring pregnancy toxemia by daily subcutaneous injection (0.15 mg/kg body weight) or a single subcutaneous injection of a slow release formulation (160 mg). It appears to improve the efficiency of glucose and ketone body usage at the cellular level, thereby reducing mortality of both the dam and the fetuses, although there was no statistical significance between treated and placebo groups warranting further studies. However, recombinant bovine somatotropin is currently not approved for extra-label use in small ruminants in the United States.

To reduce the glucose demand and effects of negative energy balance, as well as to improve the potential response to therapy, induction of parturition is often recommended in affected females. Transabdominal ultrasonography to assess fetal viability can be of benefit when considering induction of parturition if the animal is > 140 days in gestation. Various protocols have been proposed for induction
of parturition or termination of pregnancy in small ruminants. Induction of parturition or termination of pregnancy in the ewe can be achieved by administering dexamethasone (10-20 mg IM), betamethasone (10 mg IM), or flumethasone (2.5 mg IM) with parturition generally occurring 36-48 hours following administration.\(^1\) Occasionally if the ewe is < 140 days gestation, a second dose of dexamethasone may be necessary.\(^2\) The placenta maintains pregnancy in late-term ewes, so it is important to note that administration of prostaglandin F\(_2\alpha\) (PGF) alone will not result in induction of parturition or termination of pregnancy.

In does, induction of parturition or termination of pregnancy can be achieved by administration of PGF, or an analogue, with or without corticosteroid administration,\(^7,19\) because the doe is corpus luteum (CL) dependent throughout the entire pregnancy. Dexamethasone administration can hasten fetal maturation if the pregnancy is not at term through stimulation of the fetal pituitary-adrenal axis. Administration of dinoprost tromethamine (2.5-15 mg IM)\(^33\), cloprostenol (75-125 \(\mu\)g IM),\(^34\) or luprostiol (3.75-7.5 mg IM)\(^34\) will result in parturition occurring 30-48 hours following administration. Administration of dexamethasone alone in does will result in induction of parturition or termination of pregnancy, but generally occurs 48-72 hours following administration.\(^1\) It has been demonstrated previously that doses of PGF as low as 1.25 mg are luteolytic,\(^35\) although the higher doses of PGF result in a more predictable time of parturition.\(^33\) Alternatively, cloprostenol (31.25-125 \(\mu\)g) administered by intravulvo-submucosal injection has also been shown to be luteolytic\(^36\) and may be considered for induction of parturition or termination of pregnancy in goats.

If induction of parturition or termination of pregnancy in small ruminants does not result in delivery of the fetuses within 72 hours, or the animal is severely compromised, a cesarean section should be considered.\(^7\) Animals that are recumbent, obtunded, have neurologic signs, or develop renal failure have a very poor prognosis for recovery. In severe cases of pregnancy toxemia a cesarean section may be considered without induction of parturition, although dam survival rate is guarded to grave and the cost of surgery must be considered (Figure 3). Neonatal survival rate is guarded in most of these cases, however delivery of live, viable lambs or kids can result (Figure 4). Females that are managed with induction of parturition/termination of pregnancy or cesarean section should be treated with broad-spectrum antimicrobials, a non-steroidal anti-inflammatory, oxytocin, and supportive care to facilitate passage of the placenta and prevent metritis.\(^1\)

It is important for owners to understand the implications of advanced treatment options, as economic issues may limit treatment strategies.\(^7\) In cases where the animal is recumbent and unable to stand (Figure 5), euthanasia may be indicated for welfare reasons.\(^1,5\) Ewes or does that do recover from pregnancy toxemia without resultant fetal death often experience dystocia at lambing or kidding, develop a retained placenta, and have reduced lactation. Lambs or kids are frequently born dead or weak, and must be managed for potential development of hypothermia and failure of passive transfer.\(^6\)

Pregnancy toxemia should be approached as a flock or herd problem. Clinically healthy animals in a flock or herd with clinically ill animals should be assessed for potential risk factors that might predispose them to subclinical disease and a prophylactic treatment plan implemented to prevent clinical disease from developing.\(^1\) Examination of 10-15% of the animals in the flock or herd may be more financially achievable and still provide valuable information. Where possible, blood samples should be collected to evaluate BHB levels.\(^1\) Animals with elevated BHB levels should be separated and monitored closely.

Prevention of pregnancy toxemia relies on good feeding practices and husbandry. Because pregnancy toxemia occurs during late gestation, nutritional management during all stages (breeding, early gestation, and late gestation) can impact the disease.\(^4\) Prior to breeding, ewes and does should be maintained on a rising plane of nutrition (flushing) from four weeks prior to breeding to six weeks following breeding.\(^6,37\) Ideally ewes and does will be a body condition score of 3 or 3.5 out of 5 at the beginning of the breeding season.\(^4,37\) In the second and third month of gestation, ewes and does should maintain a consistent body weight and not be overfed. In the fourth and fifth month of gestation fetal growth is at its greatest,\(^6\) with fetuses acquiring up to 75-80% of their future body weight.\(^16,37\) An adequate nutritional program should be constructed in which adequate rumen-fermentable carbohydrate,
degradable protein, and fiber is provided to support rumen microbial growth.\textsuperscript{7,37} Body condition scores one month prior to parturition should be between 2.5 and 3.5.\textsuperscript{4,37} Lower quality hay can be fed in mid-pregnancy, or animals may be grazed without additional supplementation, but it should be replaced with high quality hay (ideally analyzed for nutritional content) and concentrates during late pregnancy.\textsuperscript{6,37} The addition of ionophores to the feed may also be considered during late gestation to encourage glucose production from propionate.\textsuperscript{2} Body condition should also be monitored and appropriate dietary changes made to ensure that animals are maintained at an ideal body condition score during pregnancy. In some cases forced exercise by enlarging the distance between feed and water sources could be instituted if animals are determined to be over conditioned.\textsuperscript{2,19}

Multiparous females with two or more fetuses will have a greater than 200\% increase in caloric requirements compared to females with singleton pregnancies.\textsuperscript{3,37,38} It is therefore important that ewes be evaluated in early gestation for number of fetuses and separated and fed accordingly during late gestation. There are several methods for determining the presence of pregnancy including non-return of mated ewes to estrus, transabdominal palpation, udder examination, biochemical tests (progesterone measurements, ovine interferon tau, pregnancy-associated glycoproteins) and ultrasonographic examination.\textsuperscript{37}

In previous years, serum progesterone concentrations were evaluated for pregnancy diagnosis and determination of fetal numbers in ewes.\textsuperscript{39,40} Rawlings et al. demonstrated that serum progesterone concentrations varied significantly with the number of fetuses present, and that average serum progesterone concentrations for ewes bearing one (5.5±0.3 ng/mL), two (8.0±0.4 ng/mL), or more than two (12.4±2.1 ng/mL) fetuses were significantly different between 94 to 95 days of gestation. Evaluation of the average serum concentrations for ewes carrying a single fetus or twins revealed incorrect diagnosis in 18\% and 30\% of the ewes, respectively. Additionally, evaluation of the average serum concentrations for ewes carrying twins or more than two fetuses revealed incorrect diagnosis of fetal numbers in 31\% and 59\% of the ewes, respectively.\textsuperscript{40}

Transabdominal ultrasonography allows for a more accurate determination of fetal numbers,\textsuperscript{37} as well as diagnosis of viability, growth, size, and age of fetuses. Transabdominal ultrasonography can be useful in early gestation, days 30-70, in determining the number of fetuses in order to separate animals into appropriate groups for nutritional management.\textsuperscript{37} Prior to 30 days the uterus is located in the pelvic inlet preventing good visualization using transabdominal ultrasonography.\textsuperscript{41} As gestation advances, the increase in fetal size and normal reduction of the amount of amnio-allantoic fluid prevents reliable assessment of fetal numbers.\textsuperscript{42}

Dawson et al. evaluated Alpine does at 35 and 49 days of gestation for pregnancy diagnosis and determination of fetal numbers. Pregnant does were accurately differentiated from open does in 100\% of the examinations. Sensitivity of transabdominal ultrasonography for diagnosis of single kids was 44\% and 82\% respectively, diagnosis of twins was 73\% and 89\% respectively, and diagnosis of triplets was 67\% and 100\% respectively indicating that transabdominal ultrasonography was more accurate at 49 days than at 35 days of gestation.\textsuperscript{41} These findings were consistent with a previous study performed in sheep.\textsuperscript{43} Gearhart et al. demonstrated that differentiating fetal numbers using transabdominal ultrasonography in Suffolk and Dorset ewes between 51 and 75 days of gestation was 100\% for ewes carrying a single lamb and 97.3\% for ewes carrying twins.\textsuperscript{42} While transabdominal ultrasonography is an accurate method for pregnancy diagnosis and determining fetal numbers, its accuracy can be strongly influenced by technical inexperience.\textsuperscript{38} Veterinarians must gain proper skills for use of ultrasonography to ensure that ewes or does are placed on the right nutritional support during late pregnancy.\textsuperscript{38}

Other management issues such as feed bunk space, feed availability, abrupt dietary changes, transportation, processing, weather stressors, and parasite control need to addressed and managed as well as possible.\textsuperscript{7}

Conclusion

In conclusion, pregnancy toxemia is a complex, multi-factorial disease affecting both sheep and goats. The pathogenesis of the disease is still not well understood, and additional studies are necessary to
further develop an understanding behind individual variations, genetic links, and metabolic processes that correlate to the disease.

While pregnancy toxemia has been described in the literature for decades, response to treatment remains variable. Development of precise and economic diagnostic tools will allow the clinician to adjust treatment to individual cases. The cornerstone to reducing economic losses is prevention. It is imperative for veterinarians and producers to work together to manage flocks and herds to prevent the development of pregnancy toxemia in order to reduce economic losses associated with development of the disease.

References
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Figure 1. Pregnancy toxemia in a ewe: postmortem examination of the sectioned liver with multifocal pale, friable areas demonstrating the typical gross appearance of fatty infiltration.
Figure 2. Pregnancy toxemia in a ewe: histologic section of liver demonstrating mild hepatocellular degeneration with lipid infiltration (arrows).

Figure 3. Pregnancy toxemia in a recumbent obtunded Targhee ewe at term: parturition was induced with administration of dexamethasone and cesarean section was scheduled.
Figure 4. Three crossbred lambs delivered through cesarean section from a ewe with pregnancy toxemia following induction of parturition.

Figure 5. Pregnancy toxemia in a ewe: parturition was induced with administration of dexamethasone. Postpartum the ewe was managed for recumbency and recovered following one week of supportive medical therapy.

(Editor’s note: Photographs in this manuscript are available in color in the online edition of Clinical Theriogenology.)