Doubles Troubles

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Introduction

Pregnancy toxemia is the most common late gestational metabolic derangement of small ruminants[3,9]. It is a clinical disorder with worldwide distribution and economic ramifications[3,9]. Overweight animals, animals subjected to complete fasting, and chronically undernourished animals are at highest risk[3,8]. Pregnancy toxemia is the result of insufficient available glucose and a negative energy balance resulting in the formation of ketone bodies and hypoglycemia[,7,8]. Prognosis is guarded to poor with mortality rates reported between 40-80% despite aggressive medical therapy[3,7,8,9]. Induced parturition or cesarean section may increase survival of the dam[10]. Potential sequelae include dystocia, hypocalcemia, metritis, failure of passive transfer, and death of the dam and neonates[8]. Treatment can be economically prohibitive thus management for prevention and early detection are critical for reducing both morbidity and mortality[9].

Case Presentation

An approximately 18-month-old, first parity, female Kiko doe (2208) presented to the Mississippi State College of Veterinary Medicine Food Animal Service on December 22nd, 2020, after a 1-week history of lethargy and hyporexia that was worsening despite supportive care. On December 21st, 2208 presented to the primary veterinarian and a tentative diagnosis of pregnancy toxemia was made. Treatment given included 12mls of dexamethasone and Lutalyse (dinoprost tromethamine) to induce parturition and 200ml propylene glycol orally every 12 hours. An orogastric tube was passed by the owner to facilitate oral electrolyte delivery on 12/21. Due to continued decline in condition- 2208 was referred to MSU.

On presentation, 2208 was depressed, responsive, sternal, and non-ambulatory. Her body condition score at presentation was estimated to be a 1.5 out of 5, weighing 108 pounds, with a distended caudal abdomen. 2208 was tachycardic, mildly tachypneic, and normothermic. No murmurs, cardia arrhythmias, pulmonary crackles, or wheezes were detected. Dehydration was estimated to be 8% with mildly delayed skin tent and capillary refill times. Her sclera were injected, the conjunctiva were hyperemic, and 2208 was displaying bruxism.

During transportation to the university, the cervical plug was dislodged with evidence of amniotic rupture and a fetus was engaging the cervix. No active uterine contractions were noted, and the cervix was inappropriately dilated. Scant mammary volume was noted indicating minimal colostrum production. Transabdominal ultrasound revealed one fetal heartbeat with a second suspected but undifferentiated during examination.

Stall side testing revealed hyperglycemia at 191mg/dl (normal 45-60mg/dl) and elevated venous ketones of 1.4mmol/L (normal <0.4mmol/L). Complete blood count revealed leukocytosis, elevated fibrinogen, platelets, anisocytosis, and poikilocytosis. Serum biochemistry confirmed hyperglycemia, mildly elevated AST, hypoalbuminemia, hypocalcemia, hypophosphatemia, elevated creatinine kinase, and slight icterus of the serum.

The guarded prognosis for survival of either the doe or kids was presented to the owner, and it was elected to proceed with cesarean section and hospitalization.

Pathophysiology of pregnancy toxemia

Ketoacidosis of late gestation in small ruminants can be broken into acute fasting and chronic malnutrition[3,8]. In over conditioned animals and appropriately conditioned animals,

pregnancy toxemia can be induced during periods of decreased feed intake or complete fasting for short periods of time[8,9]. When readily available sources of glucose are depleted, the body will mobilize fat reserves for lipolysis and gluconeogenesis in the liver[4,8]. Rapid mobilization of fat in the absence of structural carbohydrates can overwhelm the liver's ability to produce glucose. This results in the production of ketone bodies and can lead to hepatic lipidosis further reducing the metabolic capacity of the liver[4,8]. Acute fasting is frequently correlated to periods of environmental or psychological stress[3,9].

Over conditioned animals are at higher risk and a worse prognosis, due to the rapid mobilization of fat into the liver causing more consequential damage[4]. Over conditioned animals are also at greater risk due to large amounts of omental fat which alongside growing uterine volume further reduces expansion of the rumen. This can physically limit adequate feed intake and predispose the animal to a negative energy balance[4,8,9,10]. In the chronic undernutrition form of the disease, animals quickly deplete body reserves and begin to catabolize fat and muscle to provide glucose to meet fetal demand[8].

Regardless of the inciting cause of pregnancy toxemia, the basic metabolic pathophysiology is the same. Eighty percent of fetal growth in small ruminants occurs in the last 6 weeks of gestation[3]. During this time the total metabolic rate increases 50% in singletons and 75% in twins[3]. As compared to early gestation, late gestational energy needs may increase 23%-42% based on fetal numbers. Each fetus requires approximately 30-40 grams of glucose per day in the last 6 weeks of gestation and glucose is preferentially prioritized to the fetus rather than dam through metabolic pathways[8]. The first mechanism that drives glucose to the fetus is the low plasma glucose levels of the sheep and goat fetus in utero. The plasma concentration of the fetus is around 8mg/dl resulting in glucose readily crossing the placenta to supply fetal requirements[7].

Once in the placental tissues, glucose is transformed into fructose and stored in fetal tissues resulting in a fetal energy reserve that is not readily passed back across to maternal circulation[7].

With partitioning of glucose to the fetus, negative energy balances in the doe or ewe can rapidly result in hypoglycemia. The body begins to mobilize body energy reserves in the form of fat and proteins to provide the liver with the needed materials for gluconeogenesis[8]. Once glucose and gluconeogenic amino acids are depleted, the acetyl-CoA produced in the liver through lipolysis cannot enter the Krebs cycle due to a shortage of intermediates such as oxaloacetate[7]. Through this pathway, the ketone bodies acetoacetate, acetone, and beta-hydroxybutyrate are produced by the liver and the rumen[8]. Beta-hydroxybutyrate and acetoacetate are strong acids and when present in sufficient concentrations begin to acidify the body systemically resulting in metabolic acidosis[4,7].

Ketoacidosis initially presents in the last 1-3 weeks of gestation. Signs include anorexia, lethargy, muscle weakness, tremors, opisthotonos, and bruxism [7,8,9]. If left untreated these signs may progress to blindness, ataxia, recumbency and death[8]. In the first 24 hours, affected animals will begin to display physical signs of the disease but bloodwork abnormalities may be noted as early as 12 hours. Death can occur within 24 hours of onset of clinical signs with a majority of affected animals succumbing to the disease within 72 hours[7,9].

Reduced hepatic function may be indicated on bloodwork and is believed to be associated with hepatic lipidosis[4]. Additionally, dehydration may create a pre-renal azotemia with lipid accumulations in the kidneys further decreasing renal function[4]. Development of ketoacidosis prior to day 140 in gestation (average normal gestation length of 150 days) indicates more severe disease. Rapid diagnosis can be made through detection of urine ketones (when plasma levels exceed 0.7mmol/L), blood beta-hydroxybutyrate (BHB) levels over 0.8mmol/L, hypoglycemia,

and metabolic acidosis[4,7,9]. Hyperglycemia may indicate late-stage disease and represent fetal death or septicemia of the dam[8]. Serum beta-hydroxybutyrate levels under 0.8mmol/L is considered normal. BHB levels greater than 0.8mmol/L but less than 3mmol/L are subclinical, and levels greater than 3 mmol/L are considered clinical ketosis[7,8,9].

Environmental and physiological stress are associated with pregnancy toxemia because they can decrease feed intake[3,9]. Detecting underlying disease processes is vital to improving the overall herd outcomes[9]. Commonly noted underlying health issues include dental disease, parasitism, *Mycobacterium avium* subsp. *paratuberculosis* (Johne's Disease), Caprine Arthritis and Encephalitis Virus, *Corynebacterium pseudotuberculosis* (caseous lymphadenitis), liver abscesses, mycoplasmosis, and hoof conformation[10]. One study demonstrated 20% of pregnancy toxemia cases have concurrent hypocalcemia and another study found 100% of patients were hypokalemic in the clinical stage of the disease[4,7]. This study with the extraordinarily high incidence of hypokalemia also had a very high overall mortality rate of 86%[7]. Evaluating for underlying disease processes and systemic derangements plays an integral role in determining prognosis, initiating treatment, and addressing herd health concerns[9].

In recent years, much work has been done to evaluate biomarkers for diagnosis and as prognostic indicators. Patient-side testing including detection of urine ketones which indicate plasma ketone levels in excess of 0.7mmol/L, systemic glucose derangements (may be low, normal, or elevated), and serum beta-hydroxybutyrate of over 0.8mmol/L with clinical signs in a gravid patient remains the standard for diagnosis[4,7,9]. Hypokalemia, hypocalcemia and metabolic acidosis are common bloodwork findings. Acute phase protein changes such as haptoglobin and C-reactive proteins were not determined to be effective for differentiating case outcomes[4,5]. A

study evaluating cardiac biomarkers determined that elevation of cardiac enzymes during ketoacidosis was linked to cardiac damage and a worse prognosis[11].

Many pregnancy toxemia patients also develop insulin resistance[4]. One discussed pathway begins with the inhibition of insulin secretion through increased serum cortisol in late pregnancy. The combination of increased cortisol with the loss of inhibition of lipolysis results in induced insulin resistance. Obese does and ewes may have preexisting insulin resistance[4]. With this finding, the addition of insulin to aggressive medical treatment may improve survivability[8,9]. In an unrelated study comparing the treatment of pregnancy toxemia through oral propylene glycol versus oral glycerol, it was noted that autogenous insulin increased with administration of oral glycerol[1].

This study comparing glycerol and propylene glycol also determined that glucose levels increased more with glycerol with less increase of lactate as compared to propylene glycol. It is believed that these changes are due to how each compound is absorbed and incorporated into the Krebs cycle for gluconeogenesis. Propylene glycol is fermented in the rumen to propionic acid which is absorbed and converted to succinyl-CoA in the liver. A small fraction of propylene glycol may be absorbed intact and metabolized to lactate in the liver which is further converted to pyruvate and oxaloacetate. These three compounds can then enter the Krebs cycle and produce cellular energy. Glycerol has a more direct metabolism as it is absorbed intact into the bloodstream and is integrated into cytosolic gluconeogenesis[1]. Due to the toxic nature of propylene glycol and detrimental effects on ruminal flora, there is some evidence for preferential treatment with glycerol[1,4]. Regardless of glucogenic treatment, both options required repeated dosing as bloodwork changes were only effective for 5 hours after dosing[1]. Dosing should not exceed 6 consecutive days of therapy[1,4].

Regardless of inciting cause, the ongoing fetal energy demands exceed the ability to feed or nutritionally supplement maternal demands and maintain both maternal life and pregnancy[9]. Induction of parturition is frequently indicated to improve maternal outcomes[10].Fetuses more than 3 days from maturity are unlikely to survive[8]. Pregnancy may be induced in small ruminants by administration of a corticosteroid but will take 24-72 hours for effect[8]. Since goats are dependent on a corpus luteum throughout pregnancy, administration of prostaglandin will reliably induce labor any time after day 4 of gestation[8]. If fetuses are viable, cesarean section improves survivability[9,10]. Since the fetus cannot use ketone bodies for energy and has a high glucose demand in late gestation, maternal ketoacidosis results in decreased placental perfusion. This decreases angiogenesis and increases hypoxia genes resulting in lactic acidosis of the fetus[4]. Lactic acidosis of the fetus results in decreased birth weights, viability, and survival. Fetal survival following pregnancy toxemia is published as low as 12%[2].

Although pregnancy toxemia in small ruminants has published mortality rates ranging from 40% to 86%, survival of the acute crisis is not the end of medical management [7,8]. Common sequelae to pregnancy toxemia include dystocia, metritis, mastitis, and retained fetal membranes[4,9]. Dystocia is reported in up to 50% of cases being treated for pregnancy toxemia. The risk for retained fetal membranes, metritis, and mastitis increases with every 1 mmol/L increase in beta-hydroxybutyrate[4]. Milk production is reduced and decreased immune function increases susceptibility to other infections. Surprisingly, multiple studies report no long-term negative effects on future reproductive soundness[4,6]. Uterine involution and further cyclicity has not been determined to be delayed following resolution of ketoacidosis[6]. One incidence of pregnancy toxemia is not considered an independent risk factor for subsequent pregnancies.

While the metabolic pathways associated with the onset and treatment are complex, there are many well understood management practices that decrease risk for pregnancy toxemia[9]. A cost effective but often underutilized tool is body condition scoring (BCS). Small ruminants are scored on a scale of 1-5 with 3.5 being ideal for a female[8,10]. At this body condition score, ribs and dorsal spinous processes should be readily palpable with moderate pressure. Rumen fill and hair coats can be deceptive and visual appraisal is not a substitute for a hands-on evaluation. Animals less than 2.5/5 BCS or over 4.5/5 BCS going into late gestation are at high risk for developing pregnancy toxemia[3,8,10]. Animals should be body condition scored prior to breeding and around day 75 of gestation. It takes 6 weeks to improve 1 body condition score[10]. For over conditioned animals, reducing body condition should be done slowly throughout early pregnancy[3].

Fetal counting and confirmation of pregnancy is another beneficial tool in management of a small ruminant herd[8]. Animals can be sorted into groups based on gestational age and fetal numbers[10]. Pregnancy toxemia is most frequently seen in second parity or greater does due to a higher prevalence of singletons in first parity females, but these younger animals should also be included in fetal counting as multiples are still common[7,9]. Fetal counting should be done between day 40 and day 75 of gestation via transabdominal ultrasound[10]..

Beyond fecundity, it is also important to consider the energy density of the diet, delivery to animals, and any compromised utilization of energy[10]. Throughout gestation, as the uterine volume expands, the volume of the abdomen that can be occupied by the rumen decreases[10]. It is important not only to offer an increased volume of feed to meet fetal demand but to increase the energy density of the feed[10]. One pound of corn or high energy equivalent feed per head in the last six weeks of gestation is sufficient for most small ruminants maintained in good condition

throughout gestation[3]. It is important that a transition feed be given to prevent ruminal acidosis from transitioning too quickly[3,10]. Feeding space is also important to reduce some animals from overindulging and others falling into energy deficits based on herd hierarchy. Pre-breeding, animals should be evaluated for preventable risk factors such as external parasites, gastrointestinal parasites, liver flukes, poor hoof conformation or other treatable and preventable complications that could reduce feed intake or efficient utilization of energy[10].

Survivability increases with prevention and with early detection of pregnancy toxemia. Animals that show decreased interest in feed should be separated and fed to monitor intake; however, isolation from the herd may induce psychological stress[3]. Herd risk assessments can be done in late pregnancy by assessing a randomized sample of the herd for urine ketones[10]. If subclinical pregnancy toxemia is suspected, high energy supplementation such as oral calf electrolyte solutions can be started. Early pregnancy toxemia can be treated with oral propylene glycol, oral electrolyte solution, and induction of parturition[8,9,10]. There is evidence that oral calcium, oral potassium, and insulin supplementation may improve survival[8,9]. In animals where calcium and potassium deficits are unknown, conservative oral supplementation is generally considered safe[8]. Intensive medical intervention may also include dextrose added to intravenous fluids and correction of acid-base derangements[8]. There is evidence that flunixin meglumine (Banamine) increases survival, but the mechanism is unknown[8]. One research study also demonstrated improved outcomes with addition of 50mg sildenafil, which is believed to work by partitioning nutrients, but this is not an approved drug in livestock species[4]. Likewise, there is some evidence for use of ionophores for nutrient partitioning but a link to reduced incidence of pregnancy toxemia has not been strongly established. Despite aggressive medical intervention

this metabolic disorder continues to have a mortality rate over 40% thus making prevention of greater impact than treatment[8].

Therapeutic Interventions

A jugular catheter was placed and a cesarian section was performed under local anesthesia by placing 2208 in right lateral recumbency with supplemental flow-by oxygen. The left flank was surgically prepped using 4% chlorhexidine and 70% isopropyl alcohol. The first kid (female) was delivered then the kid engaging the cervix was delivered second (male). The uterine body, body wall, and skin was closed while a second team dried and warmed the twins. Pre-operative medications include flunixin meglumine at a 1.1mg/kg dose, and ceftiofur sodium (Naxcel) at a 2.2mg/kg dose. Post-operatively, an 8-way Clostridial booster (Covexin 8) was provided, and 1 liter of lactated ringer solution was administered IV. Number 2208 was placed in a straw bedded stall with ad libitum water, Bermuda grass hay, timothy grass hay and small amounts of alfalfa hay and grain. She was stood for 5 minutes every 4 hours overnight.

No systemic anesthesia medications were required to facilitate the surgery resulting in rapid neonate alertness and activity. Each umbilicus was dipped in betadine solution. Orogastric tubes were passed on each kid, and they were given a high-quality colostrum replacer within 30 minutes of delivery.

On day two of hospitalization, uterine contractions were observed and delayed fetal membranes were beginning to be expelled. Number 2208 remained agalactic and her kids were maintained on supplemental feeding but housed with their dam. Number 2208 weighed in at 82 pounds post-parturient and remained weak. She was continued on Naxcel and transitioned from

flunixin meglumine to oral meloxicam for post-operative inflammation. Standing was increased to every 2 hours and IV fluids were discontinued.

By day three of hospitalization, retained fetal membranes were continuing to be expelled but a dark, malodorous discharge developed. Two milliliters of prostaglandins (Lutalyse) and one milliliter of oxytocin were administered to strengthen uterine contractions and expel retained fetal membranes three times a day. Procaine penicillin G (at a dose of 44,000IU/kg) was added alongside Naxcel antibiotic therapy for improved anaerobic spectrum coverage.

Over the next several days, 2208 continued to receive intensive supportive care for weakness, metritis, and malnutrition. Physical therapy measures such as increased frequency of standing, prolonged supported standing over a bale of straw, and eventually assisted walking were added into the treatment plan for weakness and to decrease muscle wasting.

Case outcome

On December 28th, 2020, doe 2208 was discharged along with her two kids. At the time of discharge, her uterine discharge had resolved to normal lochia, her vital parameters were within normal limits, and she was able to rise independently and take 2-3 steps around the stall before laying back down. Her body condition score at discharge was 1/5. Naxcel, procaine penicillin G, and meloxicam were continued through January 4th, 2021. Both kids were apparently healthy at discharge. Nutrition recommendations were given at discharge for ad lib grass hay, ½ flake alfalfa hay, and 2 pounds of pelleted goat feed per day with ad-lib water access. A 28-day milk and meat withdrawal were given at discharge while a request was

submitted to the Food Animal Residue Avoidance Database (FARAD) for an appropriate withhold time . Skin suture removal was scheduled with the primary veterinarian.

Follow up and management

Three weeks after discharge, a follow-up farm visit was made to assist the farm in development of husbandry protocols by assessing resources, the nutrition program, and other management parameters. Doe 2208 was bright and alert and had improved to a body condition score of 3/5. She was ambulating normally with normal appetite, urination, defecation, and attitude. The doe and buck kids were bright, alert, and growing appropriately on milk replacer. Although 2208 eventually did start producing some milk, the owner elected let her dry up to give her the best chance of recovery for rebreeding in the fall of 2021.

Conclusion

Ketoacidosis of late gestation in small ruminants is a common metabolic disorder with an overall poor prognosis. Work is still being done to understand the metabolic pathways of the disease, develop new tests with prognostic value, and improve outcomes through new treatment protocols. This is a disorder of nutrition and is largely preventable through sound nutritional management practices. Often the cost of treatment exceeds the value of the animal and thus aggressive therapy is economically prohibitive. Even with early intervention and aggressive medical therapy including cesarean section, intravenous fluids, and correction of metabolic acidosis and electrolyte derangements, survival rates for either kids and/or doe are poor. Complications and sequalae including dystocia, metritis, and mastitis are common. Although

initial assessment of 2208 at intake placed a low chance of survival on either the kids or the doe, treatment proved rewarding with 100% survival to discharge.

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