CHARACTERIZATION OF SHORT- AND LONG-TERM MORBIDITY AND MORTALITY OF GOAT KIDS BORN TO DOES WITH PREGNANCY TOXEMIA

By

LESLIE F. WAGNER, DVM

Bachelor of Science in Biomedical Science

Texas A&M University

College Station, Texas

2011

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in partial fulfillment of
the requirements for
the Degree of
MASTER OF SCIENCE
December, 2019

CHARACTERIZATION OF SHORT- AND LONG-TERM MORBIDITY AND MORTALITY OF GOAT KIDS BORN TO DOES WITH PREGNANCY TOXEMIA

Thesis Approved:

Melanie Boileau DVM, MS, DACVIM

Thesis Adviser

Lyndi Gilliam DVM, PhD, DACVIM

Jared Taylor DVM, MPH, PhD, DACVIM, DACVPM

ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. Boileau, for her patient mentorship throughout this project. I also want to thank Drs. Gilliam and Taylor for sharing their expertise.

I would like to extend a special thank you to Debbie Sodowsky and Dr. Danielle Dugat for graciously bringing their healthy does to the hospital for my control group. I truly could not have gotten this project done without your kindness.

I am also grateful for the help of my colleagues Dr. Bryan M. Weaver, Arantxa Lasa, RVT, Ashley Wick, RVT, Robin Jack and Stephanie Gillham for their assistance in gathering samples from all these kids.

Lastly, I would like to thank the Agricultural Experiment Station at Oklahoma State University for providing the funding that made this project possible.

Name: LESLIE WAGNER, DVM

Date of Degree: DECEMBER, 2019

Title of Study: CHARACTERIZATION OF SHORT- AND LONG-TERM MORBIDITY AND MORTALITY OF GOAT KIDS BORN TO DOES WITH PREGNANCY TOXEMIA

Major Field: VETERINARY BIOMEDICAL SCIENCES

Abstract: Pregnancy Toxemia is a common peri-parturient disease of negative energy balance seen in sheep and goats in the last trimester of pregnancy. Although several studies have evaluated outcomes for dams with pregnancy toxemia, there is a gap in knowledge for its effects on the lambs and kids after parturition. The aim of this study was to characterize the short- and long-term morbidity and mortality of kids born to pregnancy toxemia does. A secondary aim was to evaluate common biochemical and hematologic parameters to find a difference between perinatal adaptation in kids from pregnancy toxemia dams (PT) and control kids (CON) from healthy dams. Serial measurements of blood L-lactate, glucose, beta-hydroxybutyrate, arterial blood gases, hematocrit, total protein, non-esterified fatty acids, and body weight were compared across groups over the first 72 hours of life. Long-term follow up was performed at 3 months. PT kids had a higher short- and long-term mortality compared to CON kids. PT kids were more likely to have a difficult birth, and more likely to require tube feeding due to abnormal nursing behavior. PT kids were much more acidemic and lactatemic at birth, and were less able to maintain their blood glucose compared to CON kids. PT kids were more likely to lose weight in the first 72 hours of life and this was associated with an increased risk of non-survival at 3 months. Overall PT kids showed a decreased ability to ventilate, mobilize energy substrates and adequately perfuse tissues in the peri-natal period which may contribute to their overall weakness and increased mortality. Clinically, these kids would benefit from prolonged oxygen supplementation and need to be monitored for weight gain and milk intake in the first few days of life. Weight loss in the first few days could be a useful predictor of future poor performance.

TABLE OF CONTENTS

Chapter Page

Chapter Page

LIST OF TABLES

Table Page

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Pregnancy toxemia in sheep and goats

Pregnancy toxemia (PT) represents one of the most important metabolic diseases affecting all sheep and goat populations, whether they are meat, dairy, or fiber breeds. PT typically occurs in the last 50 days of gestation, with highest incidence within the 14 days prior to parturition, when fetal growth rate (and thus energy demand) is at its peak. PT is most commonly seen in multiparous does/ewes carrying multiple fetuses[1]. With the increasing amount of abdominal space being occupied by the gravid uterus (and fat; if obese), the rumen fill becomes restricted and overall feed intake is significantly reduced. Consequently, when does/ewes cannot consume enough feed to meet the demands of fetal growth and their own homeostasis they are put into a state of negative energy balance. As a response, energy will be derived through rapid mobilization of the dam's fat stores, increasing the level of glycerol and non-esterified fatty acid (NEFA) in the circulation [2]. Rapid fat mobilization may overwhelm the capacity of the liver resulting in hepatic lipidosis. Concurrent depletion of liver glycogen stores eventually results in formation of ketone bodies: beta-hydroxybutyrate (BHB), acetoacetate, and acetone, which accumulates to a pathologic level, leading to PT (summarized in Figure 1).

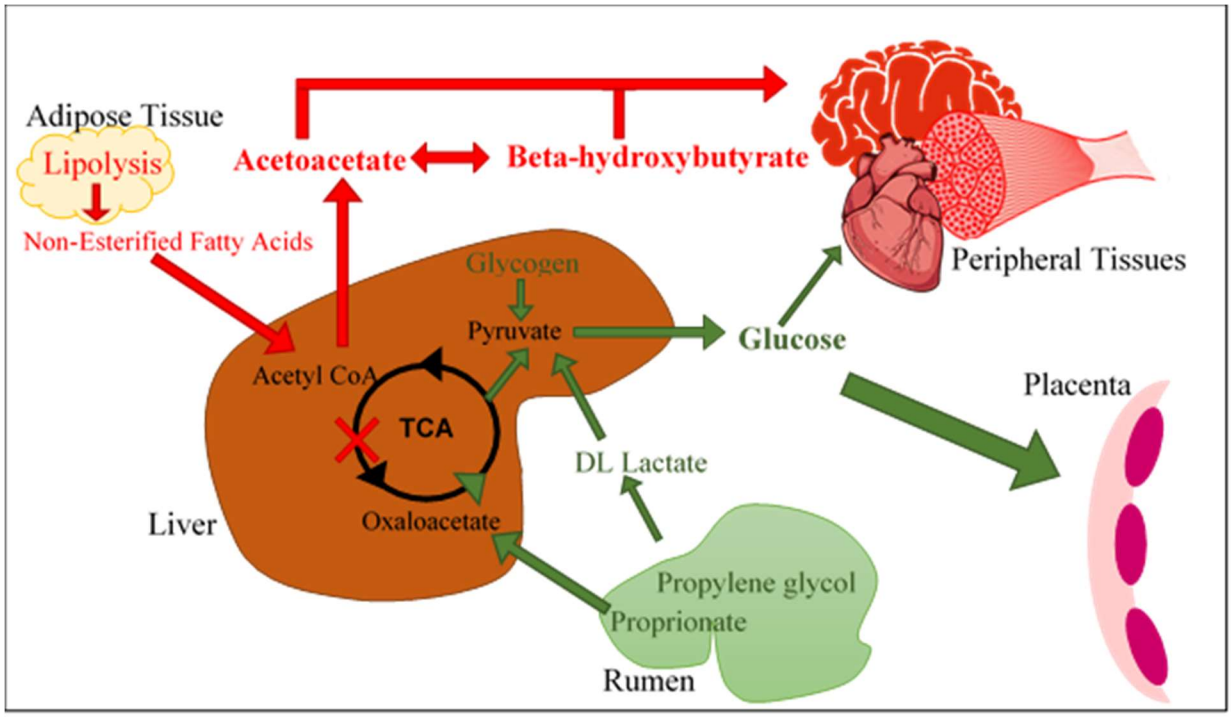

Figure 1: Metabolic pathways involved in energy metabolism when there is an adequate (green) or inadequate (red) supply of glucose or glucose precursors. TCA: tricarboxylic acid cycle (Krebs cycle)

In addition, in the last 2 to 3 weeks of gestation, progesterone level is high, causing immune suppression and a periparturient rise in internal parasites, particularly *Haemonchus contortus* and coccidia oocysts[3] as well as exacerbation of other common diseases such as pneumonia. These further increase energy requirements of the doe/ewe, which contributes to PT, and often lead to severe debilitation, premature labor, or even death of the dam and/or fetuses if not recognized and addressed promptly. Clinically, offspring of these does/ewes appear to be weak and unthrifty in the perinatal period. The prognosis is thought to be poor for these offspring. Although not much is known about the factors associated with this poor prognosis, it is suspected that the key difference may be in how they adapt to extra-uterine life.

Perinatal adaptation

At parturition several structural and physiological changes occur in fetal circulation to allow for adequate gas exchange and metabolism in the newborn goat kid. Failure of the neonate to adapt to the extra-uterine environment will result in an increased risk of failure of passive transfer of immunoglobulin from maternal colostrum, a higher likelihood of hypothermia and increased morbidity and mortality secondary to infectious diseases[4]. Dystocia and neonatal hypoxia are known to compromise such adaptations[4], however, the role that PT and poor placental nutrient transport play during late gestation are unknown at this time.

While in utero, the placenta is the major organ for exchange of both carbon dioxide (CO_2) from the fetal circulation and oxygen (O_2) from the maternal circulation. Oxygenated blood is carried in the umbilical vein to the fetal portal vein and shunted to the caudal vena cava through the ductus venosus. After being emptied into the right atrium of the fetal heart, about half of the blood is shunted through the foramen ovale into the left atrium where it is transported to the tissues to provide them oxygen and nutrients. Due to the relative hypoxic intra-uterine environment, the pulmonary vessels remain constricted. This increase in pulmonary vascular resistance contributes to further shunting of oxygenated blood away from the non-functional fetal lungs via the ductus arteriosus from the pulmonary artery. Two umbilical arteries carry venous blood from the fetal circulation to the placenta for exchange of waste products[4].

At the time of birth, when the umbilical cord ruptures hypoxia of the neonate triggers a gasping reflex. Mechanical ventilation encourages opening of collapsed alveoli and absorption of fluid across the respiratory epithelium. The opening of aveoli causes a decrease in pulmonary vascular resistance. Increased oxygen saturation of the blood in the pulmonary artery stimulates closure of the ductus arteriosus within 4-5 minutes of birth. Increased pressure within the left atrium will stimulate closure of the foramen ovale within 5-20 minutes. There is a mild, transient

metabolic and respiratory acidosis seen in healthy calves following rupture of the umbilical cord due to anaerobic glycolysis in the tissues and poor tissue perfusion[5]. Normal arterial blood gas values for newborn calves and foals can be seen in Table 1.

Species	**Age**	**pH**	**pO_2 (mmHg)**	**pCO_2 (mmHg)**	**HCO_3 (mmol/L)**
Bovine [6]	1 hour	7.3 ± 0.05	58.43 ± 11.61	50.4 ± 5.27	23.52 ± 2.78
Equine [7]	0-1 hour	7.2-7.3	40-50	52-60	24-26
Equine [7]	Premature (1hr)	7.33	52 ± 4	48 ± 3	25 ± 1
Equine [7]	2 hours	7.37 ± 0.01	68 ± 10	49 ± 2	26 ± 2

Table 1: Arterial blood gas in newborn calves and foals. Adapted from Smith[4]. All subjects were in lateral recumbency. Values expressed as mean ± standard deviation where available.

Neonatal energy substrates

In utero, energy must be derived through placental transport. The placenta utilizes 50-70% of the glucose and oxygen delivered to the uterus and transfers the remainder to the fetal tissues[8]. Placental transport efficiency of glucose to the fetus is influenced by placental size, number of placentomes, vascularization, and abundance of GLUT 1 and 3 transporters. These characteristics are mediated by both maternal and fetal genomic regulation[8]. The placenta also produces lactate for fetal energy use as well as gluconeogenic amino acids through transamination and deamination processes[8]. Although the enzymes for gluconeogenesis are present early in fetal development, the fetus will only produce its own glucose under extreme conditions such as maternal starvation[9].

In the post-partum neonate, energy is derived by the metabolism of brown fat. Normal blood glucose concentrations in calves at birth are lower than juvenile reference values (80-120 mg/dL), but rise to >100 mg/dL within the first 24 hours[10]. Newborn human infants also experience low blood glucose levels as they adapt to extra-uterine life, but rise and stabilize by 2-3 hours post-partum[9]. In normal foals, baseline blood glucose values immediately post-partum were approximately half of the maternal blood glucose value, and continues to decline while the foal transitions to extra-uterine life, reaching a low around 2 hours of age[11]. Any delay in colostrum consumption, due to neonatal weakness or ill health of the dam, decreases the availability of energy substrates and can lead to potentially fatal hypoglycemia. The main sources of energy available to the neonate are glycogen, lactate, brown adipose fat, and proteins.

Neonatal production of glucose is achieved primarily by glycogenolysis in the liver and is under hormonal control. This process is stimulated by increases in catecholamines and glucagon, and decreases in insulin which occur during delivery[12]. There are limited stores of glycogen within the neonatal liver, however, and once exhausted the neonate must rely upon lactate, pyruvate, glycerols, and alanine for gluconeogenesis. The rate-limiting enzyme for gluconeogenesis is phosphoenolpyruvate carboxykinase (PEPCK) which has limited activity in the fetus but shows marked increases soon after birth possibly in response to a decrease in the insulin:glucagon ratio[13]. Neonates are also capable of converting lactate into glucose rather efficiently through the hepatic Cori cycle. Lactate accounts for up to 30% of hepatic glucose production in the first day of life, whereas alanine and glycerol typically represent 5-10% each. Additionally, lactate can serve as an energy substrate for the brain and thus has a glucose-sparing effect in the neonatal metabolism[14]. Although the neonate has a tremendous ability to produce its own glucose, this alone is not sufficient for energy production, particularly if nursing is delayed.

The second major energy source for neonates is brown adipose tissue, comprised of triacylglycerols (TAGs). The fat stores are primarily formed during the latter third of gestation

and in a full-term human neonate correlates to about 15% of its birthweight[9]. Neonates have a temperature dependent increase in thyroid stimulating hormone immediately post-partum which causes a high rate of lipolysis[15]. The hydrolysis of TAGs results in an increase in the circulating NEFAs and glycerol. Glycerol can be used for gluconeogenesis and NEFAs are converted to ketone bodies via β-oxidation in the liver. Ketone bodies can cross the blood-brain barrier and act as an additional energy source for the brain. In human infants, ketone body formation and metabolism has been shown to be an active process[16]. The effective use of both lactate and ketone bodies as alternate energy sources could explain why some neonates have low blood glucose concentrations but do not display classical signs of hypoglycemia such as weakness, depression, and neurologic dysfunction.

Protein catabolism can also provide energy for the neonate. Studies of human infants have shown that protein metabolism is particularly important in extremely low birthweight infants[17]. This could be, in part, due to a lack of significant fat depots. Regardless of birthweight, proteins can provide substrates for gluconeogenesis and the turnover of the essential amino acid, leucine, has been shown to be much higher in infants when compared to adults [17].

CHAPTER II

REVIEW OF LITERATURE

Fetal programming and maternal undernutrition

Fetal programming relates to how the uterine environment impacts the development and physiology of the fetus resulting in different outcomes, positive or negative, for offspring later in life[9]. In a study of ewes with experimentally induced PT, nutrition was steadily decreased between each trimester of gestation. Clinical signs associated with PT, as well as increased blood BHB levels, were seen in 16/28 (57%) ewes. In this study, they found a significantly higher lamb mortality from PT ewes than non-PT ewes and a negative correlation between blood BHB concentrations and lamb birth weight[3]. They hypothesized that the higher mortality of lambs due to PT was attributed to growth retardation in the uterus from poor nutrition of the dam[18]. While many studies have shown that clinical PT does can be hyper- or normoglycemic,[1,19-21] others have shown that PT does tend to be hypoglycemic compared to controls.[22,23] One study found that hyperglycemia may be a sign that the fetuses are no longer viable in advanced PT does.[24] A study that looked at pregnant ewes with 1-4 fetuses saw that blood glucose decreased with increased fetal number and this relationship began before the study period of 5 weeks prior to lambing. This suggests that the alterations in maternal glucose appear earlier than clinical disease, and that by the time clinical PT is present the blood glucose is more variable depending on the degree of glucose dysregulation. In times of short-term maternal hypoglycemia,

the placenta will decrease its glucose utilization to maintain the same proportion of glucose transport to the fetal tissues[25,26]. However, when the maternal hypoglycemia is prolonged (>3 weeks), the placenta will increase utilization of glucose for itself and proportionally decrease glucose transport to the fetal tissues[27]. Maternal hypoglycemia will also decrease placental production of lactate and the metabolism of amino acids for fetal gluconeogenesis[8]. A study that explored gene expression of the uterus and placenta in subclinical PT ewes found that there was a significant decrease in the expression of genes responsible for vascularization of the placenta and an increase in the genes that respond to placental hypoxia[28]. These hemodynamic changes affect the rate of transplacental nutrient exchange, decrease fetal growth, and impact health of the dam. Other studies have correlated poor nutrition to altered development of the heart[29,30], lungs[31], and the pancreas[32]. The dysfunction of these organs in newborns and fetuses can result in death, a failure to thrive, and an increased susceptibility to infections[33].

It has also been shown in animal and human models that the glucose-insulin homeostasis of the dam can have both short- and long-term effects on the energy metabolism of the neonate. Women with gestational diabetes typically experience hyperglycemia, with decreased insulin sensitivity and decreased pancreatic β cell function. As a result of the hyperglycemia, the infant is born with increased levels of insulin and a tendency towards hypoglycemia[9]. Even in well-controlled diabetes, the infant is born with a lower glucose production and a higher insulin concentration compared with normal full-term infants. Interestingly, the insulin in these infants does not inhibit their rate of lipolysis[9]. Ewes/does with PT have similar alterations in their glucose-insulin homeostasis. Ewes with PT, or at high risk for PT, have been shown to have a relative insulin resistance, higher baseline lipolysis, and impaired insulin:glucagon ratios[34]. In another study, dairy goats with PT had a marked glucose intolerance after an oral glucose challenge when compared to high producing pregnant and non-pregnant does[35]. Neither study looked into the metabolism of the offspring born to these dams and whether their glucose

regulation was altered as seen for human infants. In cattle, nutrient restriction of the cow in late gestation has been shown to alter glucose tolerance and clearance of her offspring[36]. Likewise, lambs born to ewes fed 50% of energy and protein requirements during late gestation had permanently depressed insulin sensitivity. Although the ewes in this study did not have clinical PT, it exemplifies how pre-natal undernutrition, a significant component of PT pathogenesis, had a significant influence on metabolic processes of the offspring later in life[37].

In human infants, birthweight and gestational age have also been associated with altered energy metabolism. Low birthweight infants have a decreased insulin sensitivity in their livers and an increased insulin sensitivity in their peripheral tissues[38,39]. In pre-term infants, the capacity for ketone body production is lower making them more dependent on glucose production for their energy needs, particularly as an energy source for the brain[9]. Gluconeogenesis occurs with the same efficiency in both full-term and pre-term human infants[39]. However, immature infants have lower stores of energy substrate and are at a higher risk for hypoglycemia. The dysregulation of glucose in this group of infants also makes them susceptible to hyperglycemia[40].

Neonatal Maladjustment Syndromes

Maladjustment to extra-uterine life can be brought about by hypoxic-ischemic injury during the peri-parturient period. In foals, the clinical syndrome of neonatal maladjustment or perinatal asphyxia can cause dysfunction of the nervous system, kidneys, gastrointestinal tract, or cardiopulmonary systems. Neonatal encephalopathy (NE) is the most commonly recognized consequence of neonatal maladjustment in foals[4]. NE occurs in animals and humans and is believed to be a result of hypoxemia of the cerebral tissues during any of the ante-partum, peri-partum, or postnatal periods. Specific risk factors recognized for peri-natal hypoxemia in infants include many causes of decreased placental blood flow and nutrient exchange such as maternal

systemic hypotension, maternal cardiac arrest, clotting of the placental arteries, placental abruption, uterine rupture, and inflammation[41]. In horses, the condition is often related to either acute or chronic hypoxia and associated with dystocia, cesarean section, premature placental separation, or placentitis[42] as well as conditions causing poor tissue oxygenation such as sepsis, prematurity, and dysmaturity[43]. There are no specific clinicopathologic abnormalities associated with neonatal maladjustment syndromes in foals, however a low pre-suckle blood glucose (<35-30 mg/dL) has been shown to be associated with placental insufficiency and increased incidence of NE in foals[44]. Additionally, there may be acidosis with a pH <7.3 and bicarbonate <20 mmol/L, and respiratory depression can cause hypoxemia (PaO2 < 60 mmHg) and hypercapnia (PaCO2 > 65 mmHg)[45].

Offspring of PT dams share several clinical signs and risk factors with foals and infants that have NE. PT offspring are commonly weak and dull, with poor nursing or udder seeking behavior. Dams with PT have an increased incidence of dystocia and other peri-partum disorders which creates an increased risk of perinatal hypoxia in PT offspring[18]. Furthermore, changes to the gene expression of the uteroplacental unit of subclinical PT ewes point to a chronic *in utero* hypoxia brought about by improper vascularization and decreased placental gas and nutrient exchange[28]. The only biochemical and hematologic study of PT offspring was performed *in utero* examining the oxygen-poor blood returning to the placenta from the fetus. They found that PT fetuses were significantly more acidemic, with lower red blood cell count, hemoglobin concentration, partial pressure of oxygen and oxygen saturation, and higher CO2 and lactate concentrations compared to fetuses from healthy does. Additionally, the PT fetuses had significantly lower glucose and higher BHB concentrations in their cord blood. They postulated that PT fetuses could have issues with hemoglobin oxygen transport as well as lactate metabolism[20]. To date, no study has reported on whether these specific hematologic and biochemical differences continue after birth.

Morbidity and mortality

Morbidity and mortality in PT offspring is scarcely reported in the literature. Barbagianni described an increase in perinatal mortality for PT lambs (37.5%) compared to control lambs (8.3%)[18]. However, this study only looked at mortality up to 2 days of age, and no further assessment of the lambs or therapeutic interventions were performed. The same study showed an increase in dystocia for PT ewes (50%) compared to controls (8.3%). When outcomes of PT were studied in dairy goats a high dam case fatality was found, and there was an increase in kid survival if induction of parturition or cesarean section was performed[24]. The maternal mortality described throughout the literature is variable but can be as high as 100%[21,24] (See Table 2).

Author	Group	Dam Mortality	Kid/lamb Mortality
Barbaggiani, et al 2015		-	37.5%
Duehlmeier, et al 2013		4/5 (80%)	-
Lima, et al 2012		19/22 (86%)	-
Lima, et al 2012[a]	All dams Hypoglycemia Hyperglycemia	9/10 (90%)	 0/14 (0%) 13/14 (93%)
Lima, et al 2016[b]	 C-section Induced	 10/10 (100%) 14/22 (64%)	 2/5 (4%) 16/26 (61.5%)
Tharwat, et al 2014		18/30 (60%)	20/74 (27%)
Kotb, et al 2015		6/9 (67%)	-
Balikci, et al 2009[c]	 Subclinical Clinical	 0/11 (0%) 4/15 (27%)	 - -
Zamir, et al 2009[d]	 2000-2004 2005-2008	 47/60 (78%) 10/83 (12%)	 50% 31%
Simpson, et al 2019		17/56 (30.4%)	50/137 (36.5%)
Wagner, 2017[e]		11/49 (22.4%)	61/132 (53.8%)

Table 2 Summary of referenced literature reporting mortality of PT dams/offspring. Data expressed as proportions where available and percentages.

[a]Hypoglycemia group includes clinical PT does with blood glucose between 1.27-2.37 mmol/L and hyperglycemia group includes clinical PT does with blood glucose between 6.16 – 21 mmol/L.

[b]Groups denote clinical PT dams that either had a cesarean section performed or were induced on presentation.

[c]Groups were classified as subclinical and clinical based on blood BHB levels.

[d]Dams grouped by study years where dams from 2005-2008 received flunixin meglumine as part of treatment protocols and dams from 2000-2004 did not.

[e]Unpublished data from a medical records review at Oklahoma State University Veterinary Teaching Hospital of all PT cases treated during 2012-2017.

Objectives

The objectives of this study was to measure the morbidity and mortality of offspring associated with PT in both the short- and long-term. A secondary objective was to measure key biochemical parameters reflective of energy metabolism and neonatal adjustment to extra-uterine life (blood glucose, BHB, L-lactate, NEFA, arterial blood gases) within the first 3 days after birth to understand the effects PT might have on offspring.

CHAPTER III

METHODOLOGY

Animal Selection

This study was performed using kids born to does with clinical PT (defined as a blood BHB >1.2 mg/dL) being treated at the Oklahoma State University Veterinary Teaching Hospital in Stillwater, Oklahoma. Control (CON) kids were provided by healthy, multiparous late pregnant does, defined as a blood BHB <1.2 mg/dL and normal physical exam findings. PT kids were enrolled from January 2018 through November 2018 and CON kids were enrolled October 2018 through May 2019. Prior to parturition all PT does were medically managed as each clinician saw fit based on severity of clinical signs, ketonemia, and glycemic status. All parturition events, for PT and control does, occurred at the teaching hospital and were attended by at least one of the authors (LW). Parturition was characterized as a normal vaginal delivery (no assistance needed), assisted vaginal delivery (one of more kids required manual traction for delivery), or cesarean section by the attending clinician. The birthing was considered a dystocia if either an assisted vaginal delivery or cesarean section were required for the birth of that particular kid. All live kids were enrolled separately into the study at the time of parturition. Immediately thereafter, the dam's health status (PT or CON), whether the dam was induced, days from expected due date (if known to be premature), delivery type, breed, gender, total number of kids delivered, number of kids born alive, stillborn, or with birth defects were all recorded for each parturition event.

Sample Collection and Analysis

At time 0 hours, approximately 3 ml of venous blood was collected from the jugular vein of each goat kid and placed into a tube containing no anticoagulant. The blood was allowed to clot, centrifuged at 3500 RPM for 5 minutes, and the serum (1 ml) separated off into a cryo-vial to be stored at -20°C until analysis for NEFAs could be performed by colorimetric enzymatic method using a commercially available assay (Cornell University Animal Health Diagnostic Center, Ithaca, NY). Arterial blood was collected at time 0 and 72 hours from the median artery while the kid was restrained in an upright position using a 1 ml reduced heparin arterial blood gas collection kit (Carefusion). Arterial blood was capped after collection and immediately analyzed using a commercially available handheld blood analyzer (VetScan i-STAT 1). Venous blood (2 ml) was collected from the jugular vein at times 0, 12, 24, 48, and 72 hours and divided equally into 1 ml tubes containing heparin and potassium EDTA. Blood glucose and L-lactate were analyzed using point-of-care meters (Precision Xtra, Abbott Diabetes Care, and Lactate Pro, Arkray) at times 0, 12, 24, 48, and 72 hours. The point-of-care meters were used according to manufacturer instructions, and no specific calibrations were performed. The rate of change in lactate was calculated as the difference between the blood lactate at 0 hours and 12, 24, 48, or 72 hours divided by the number of hours between measurements. Blood BHB was analyzed using a point-of-care meter previously validated for use in goats (Precision Xtra, Abbott Diabetes Care)[46]. Packed cell volume (PCV) and total protein (TP) was measured by filling a microhematocrit tube with blood from the EDTA tube and centrifuging at 9500 rpm for 7 minutes. The plasma TP was measured by optical refractometry. PCV and TP were performed at times 0, 24, 48, and 72 hours. Failure of passive transfer was defined as a TP less than 5.4 g/dL at 48 hours of age[47]. Weights for each kid were collected at times 0, 24,48, and 72 hours using an electronic scale. Daily gain (DG) was calculated as the difference between weights at time 0 and 24, 24 and 48, and 48 and

72 hours. The average daily gain (ADG) was calculated by dividing the difference between weights at time 0 and 72 hours by 3.

Morbidity and Mortality

Goat kids were monitored each hour for nursing activity. If colostrum was unable to be obtained from the dam, a commercial bovine immunoglobulin colostrum replacer (Calf's Choice Total HiCal, Alta Genetics Inc.) was given by bottle or orogastric intubation at 10% body weight over the first 12 hours. At times 0 and 12 hours, it was recorded whether colostrum was readily nursed off the dam, tube fed, or bottle fed. The source of colostrum was recorded as either all from the dam, supplemented with colostrum replacer (mixed), or entirely provided by colostrum replacer. Nursing behavior was evaluated by one of the investigators (LW) and recorded at times 0 and 12 hours. Abnormal nursing behavior was defined as the inability or lack of desire to latch onto and suckle either the dam's teat or the nipple of a bottle after 30 minutes of assistance, subsequently requiring orogastric intubation for the administration of colostrum. Short-term morbidity and mortality were evaluated at times 0, 12, 24, 48, and 72 hours. Short-term morbidity was defined by three categories: normal (independently active and nursing well), moderate (weak/poor suckle, assistance needed to nurse the dam or a bottle), or severe (unable to stand, no suckle, tube feeding required, unable to regulate body temperature). If death occurred within the first 72 hours, mortality was recorded at the next measurement time point (0, 12, 24, 48, or 72 hours). Long-term morbidity and mortality was obtained by follow up phone conversations with the owners at 3 months of age. Long-term morbidity was defined as either successful fulfillment of the animal's purpose (kept or sold as a breeding animal or as an exhibition animal) or early culling due to poor performance.

Statistical Methods

Power calculations were performed with the following assumptions: alpha =0.05, ratio of approximately one control kid for each kid born to a PT doe; beta of 0.2 (power of 80%). The anticipated number of enrollees provides a greater than 90% probability of detecting significant differences of 0.1 in blood pH, base excess, and $PaCO_2$ (assuming standard deviations within each population of 0.1 for each parameter). All data was analyzed using JMP Pro 14 (SAS Institute Inc., Cary, NC). All descriptive statistics were reported as mean ± SEM. All continuous variables were tested for normality using the Shapiro Wilk test. Normally distributed data were analyzed using a paired t test. Non-parametric continuous data were analyzed using the Wilcoxin Rank Sum Exact test. Categorical variables were analyzed using a Fisher's Exact test. Relative risks were calculated where there were two levels of categorical data and were recorded with 95% confidence intervals. Comparisons were made for all variables between kids born to PT does and kids born to control does. Kaplan-Meier plots, with right-censored data, were used to show differences in survival between kids born to PT/Control does. The Wilcoxon test was applied to survival between groups in order to put emphasis on early survival times. All parameters were compared between the kids born to PT does surviving and non-surviving kids at 72 hours and 3 months using either a student's t test or Wilcoxon Rank Sum Exact test as described earlier. Repeated measures were analyzed using a mixed model approach with time, doe PT status, and two and three way interactions (time and PT status (time*PT), and time over time and doe PT status (time*time*PT)) as fixed effects and individual kid and dam as random effects. Values of $p < 0.05$ were considered significant with Holm-Bonferroni correction for multiple comparisons.

CHAPTER IV

FINDINGS

Dam BHB status and parturition factors

A total of 16 kids were enrolled from 6 does with clinical PT, and 12 kids from 6 control (CON) does. All PT and CON does were multiparous. All does and kids were Boer, and there was no significant difference between the distribution of male (9/16 PT and 5/12 CON) and female (7/16 PT and 7/12 CON) kids between the two groups (p=0.7036). Parturition was induced with intramuscular injections of 10 mg of dexamethasone and 10 mg of dinoprost tromethamine in 4/6 PT does and 0/6 CON does. PT does had a significantly higher BHB than CON does (4.44 ± 3.71 and 0.6 ± 0.09 mmol/L, $p < 0.0001$). There was no significant difference in either total number of live or stillborn kids per parturition event, and none of the kids in the study had any congenital defects. The mean days before expected due date for the PT does was 8.8125 ± 1.89 days with a range of 2-21 days. PT does also had an increased incidence in assisted delivery and cesarean sections compared to CON does. ($p = 0.152$). The relative risk of dystocia given a doe had PT was 1.625 (95% CI [0.88,3.00]).

Blood Lactate

There was a significant interaction between doe PT status and time for serial measurements of blood L-lactate. L-lactate levels were significantly higher in PT kids compared

to CON kids at sampling times 0 and 12 hours (p = 0.018 and 0.0061, respectively). Mean ± SEM lactate levels for both groups of kids are presented in Figure 2.

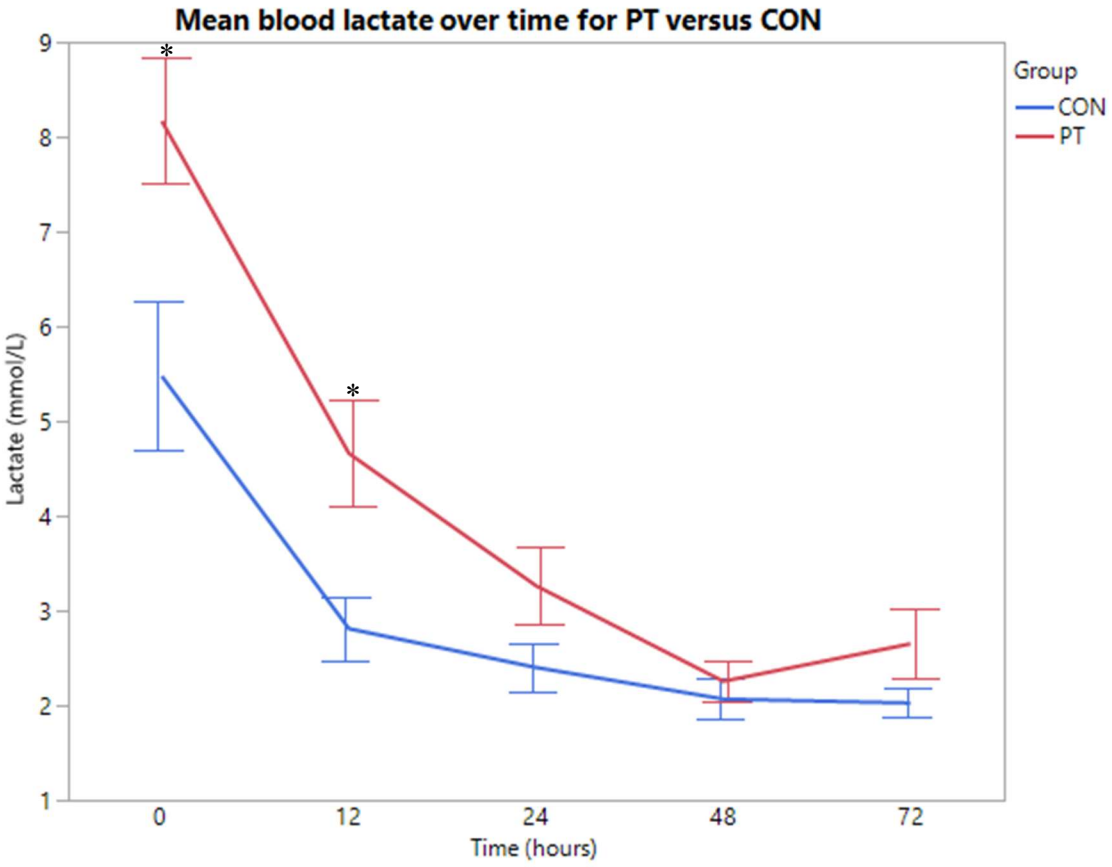

Figure 2: Mean blood L-lactate values time for PT versus CON groups. Each error bar represents 1 standard error from the mean.
** denotes significant difference between groups at that time point (p<0.05)*

Blood Glucose

In the mixed model, there was a significant interaction between doe PT status and time. There was a significant difference between PT and CON groups at sampling times 24 and 72 hours (p = 0.0384 and 0.0063, respectively). Mean ± SEM for blood glucose are presented in Figure 3.

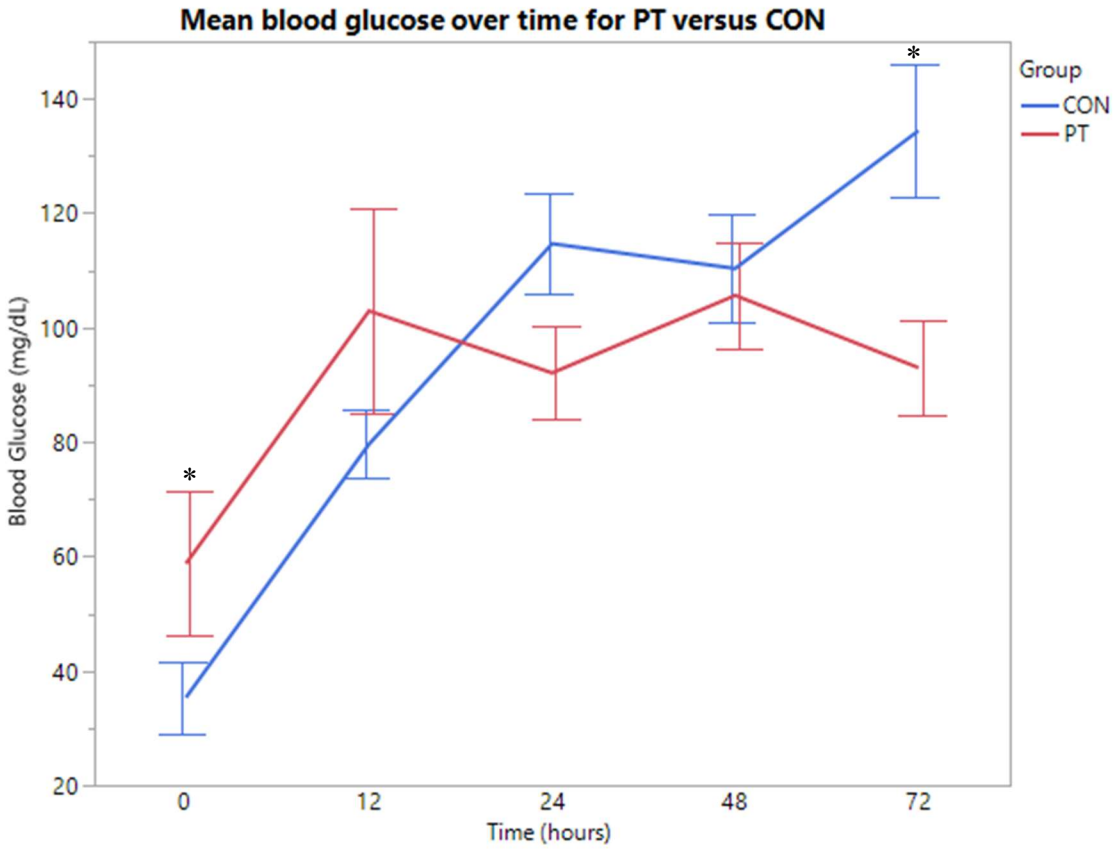

Figure 3: Mean blood glucose values graphed over time for PT versus CON kids. Each error bar represents 1 standard error from the mean
** denotes significant difference between groups at that time point (p<0.05)*

Beta-hydroxybutyrate

There was a significant interaction between time and PT status in the mixed model. The only time point where blood BHB differed between the two groups was at time 0 when PT was significantly greater than CON (0.93 ± 0.019 mmol/L and 0.008 ± 0.008 mmol/L, p = 0.0159) (Figure 4).

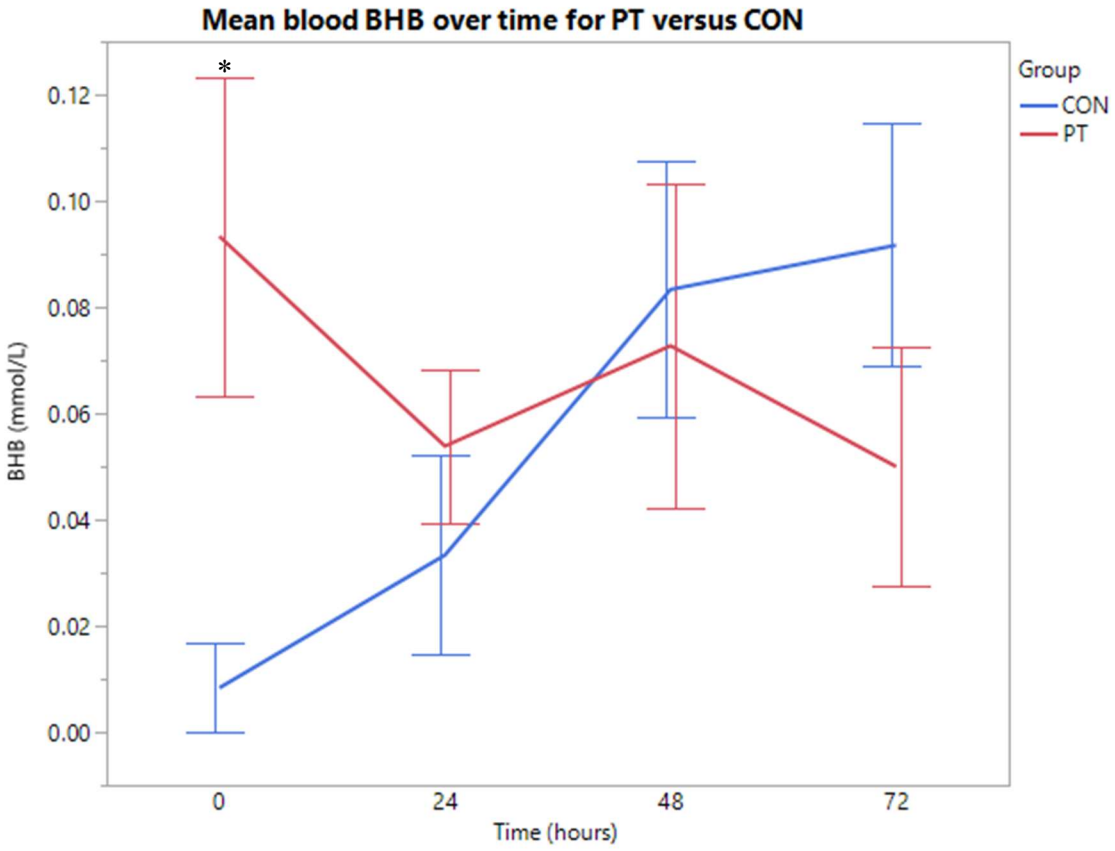

Figure 4: Mean blood BHB over time for PT versus CON. Each error bar is constructed using 1 standard error from the mean.
** denotes significant difference between groups at that time point ($p<0.05$)*

Non-esterified fatty acids

There was no significant difference between NEFA measurements in PT (0.318 ± 0.058 mEq/L) and CON (0.328 ± 0.077 mEq/L) groups ($p = 0.32$).

Arterial Blood Gases

There was a significant interaction between time and PT status for repeated measurements of arterial pH, base excess (BE), bicarbonate (HCO_3), and total carbon dioxide (TCO_2). The partial pressures of carbon dioxide ($PaCO_2$) and partial pressure of oxygen (PaO_2) decreased over time, but there was no significant effect of PT status for either variable. Oxygen

saturation (SO_2) increased over time in both groups, but the sO2 for PT kids was significantly lower across the study period (p = 0.0490).

Mean pH for PT and CON kids were significantly different for both 0 and 72 hours. However, they differed in how they were related at each time. The PT group showed an increase in blood pH from time 0 and 72 hours. The CON group also showed an increase from time 0 and time 72 hours. However, the PT group was initially significantly more acidemic than the CON group immediately after birth but, by 72 hours of age, tended to be more alkaline than the CON kids (Figure 5).

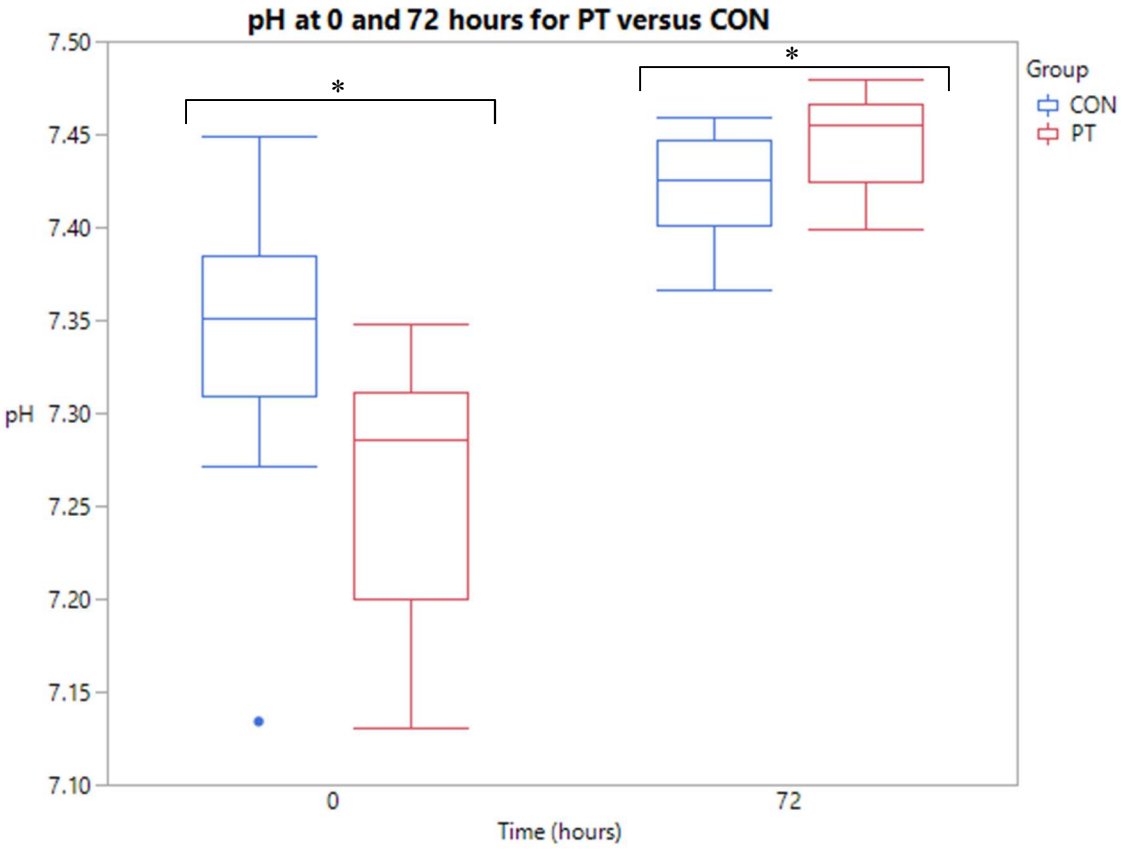

Figure 5: Blood pH at 0 and 72 hours for PT versus CON.
** denotes significant difference between groups at that time point.*

Values for BE, HCO3, and TCO2 were all significantly decreased in PT vs CON kids at time 0. After 72 hours of age, all variables were significantly increased in PT as compared to CON

group. Sodium levels were significantly higher in CON compared to PT at time 0, but not significantly different at 72 hrs. All arterial blood gas and electrolyte values are presented in Table 3.

	Time = 0 hrs			Time = 72 hrs		
	PT	CON	p-value	PT	CON	p-value
pH	7.26 ± 0.019	7.34 ± 0.023	0.0027*	7.45 ± 0.008	7.42 ± 0.008	0.0456*
Base Excess	-5.8 ± 0.99	-1.8 ± 1.07	0.0114*	3 ± 1.11	-1.7 ± 1.03	0.0025*
HCO_3^- (mmol/L)	22 ± 0.77	24 ± 0.81	0.016*	27 ± 1.02	23 ± 1	0.0049*
TCO_2 (mmol/L)	23 ± 0.79	25 ± 0.8	0.024*	28 ± 1.03	24 ± 1.07	0.0060*

Table 3: Arterial blood gas and values for PT and CON kids at times 0 and 72 hours. All values expressed as mean ± SEM.
**p<0.05*

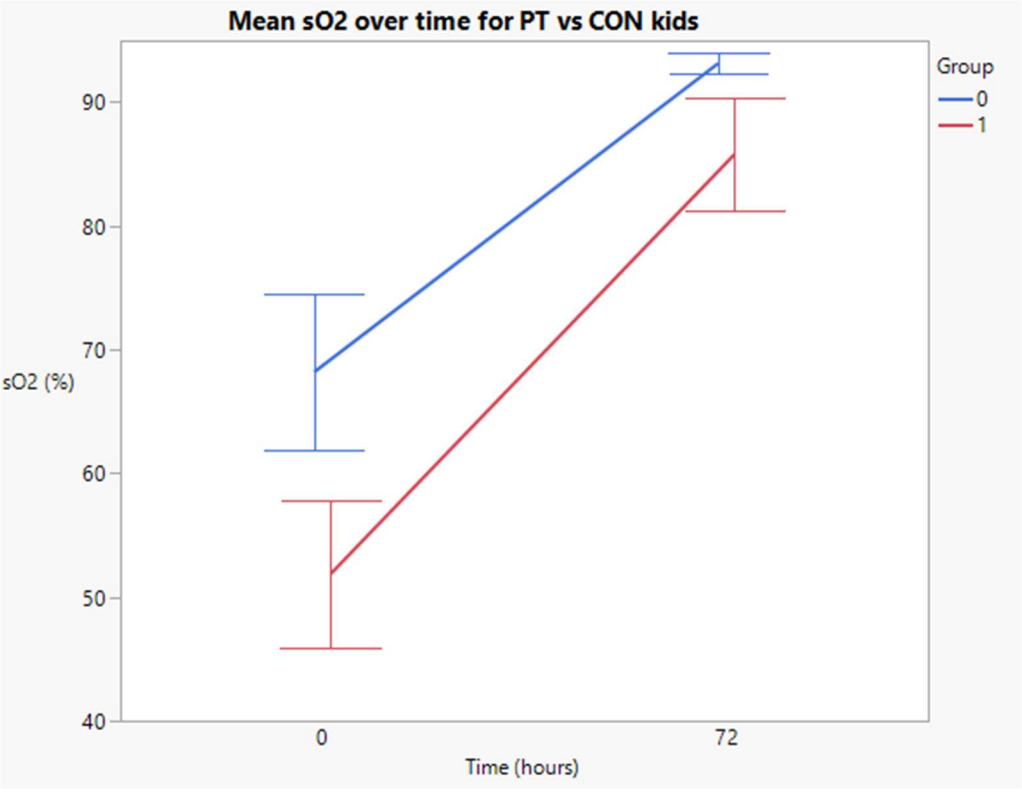

Figure 6 Mean sO2 over time for PT vs CON kids. Both groups trended up during the study period, however, PT kids had significantly lower values in the mixed model.

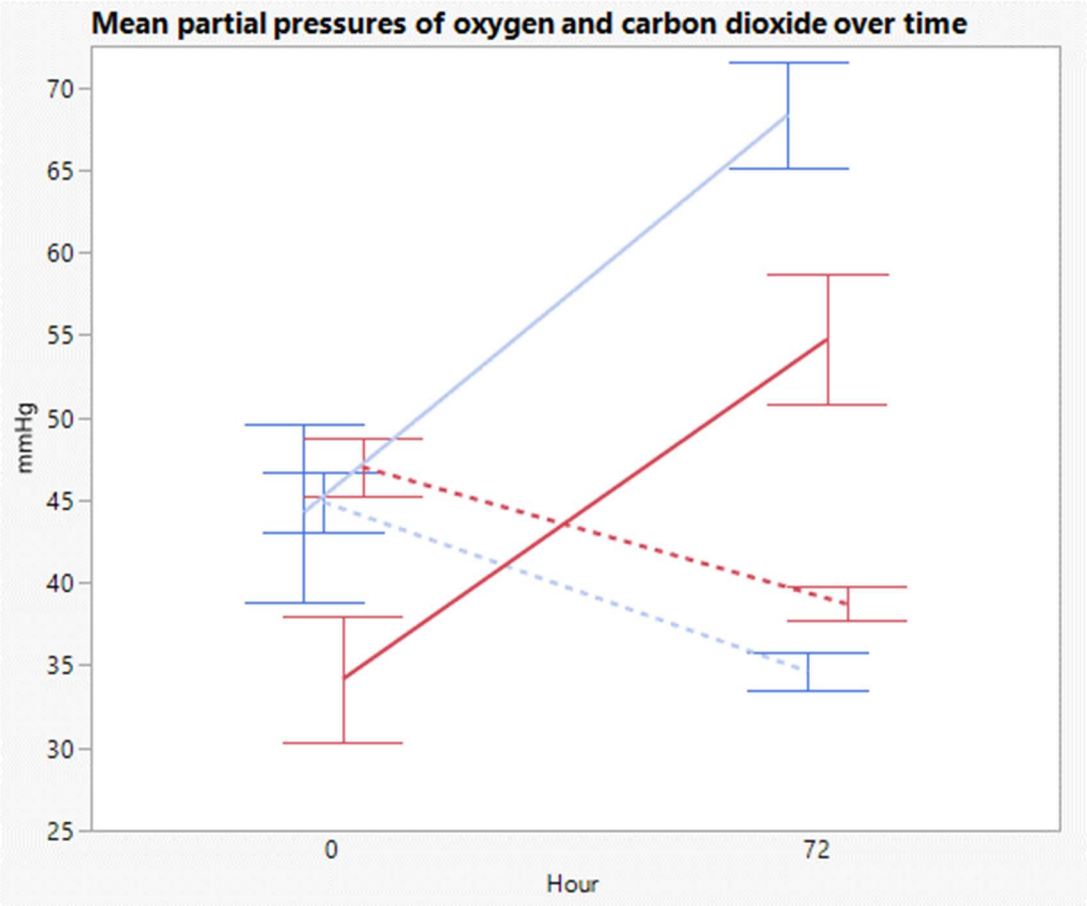

Figure 7 Mean Partial pressures over time for pCO2 (dashed lines) and pO2 (solid lines) for PT kids (red) vs CON kids (blue). There was a significant but opposite effect of time for both of these variables, but PT status did not show a significant effect.

Packed Cell Volume and Total Protein

In the mixed models for PCV and TP, there was a three-way interaction of time*time*PT status. There was a significant maternal effect on PCV ($p = 0.0492$). PCV was significantly lower for PT vs CON kids at all time points it was measured (Figure 6). Total protein was also significantly lower for PT vs CON kids at 24 and 72 hours ($p = 0.0005$ and 0.0206, respectively) (Figure 7).

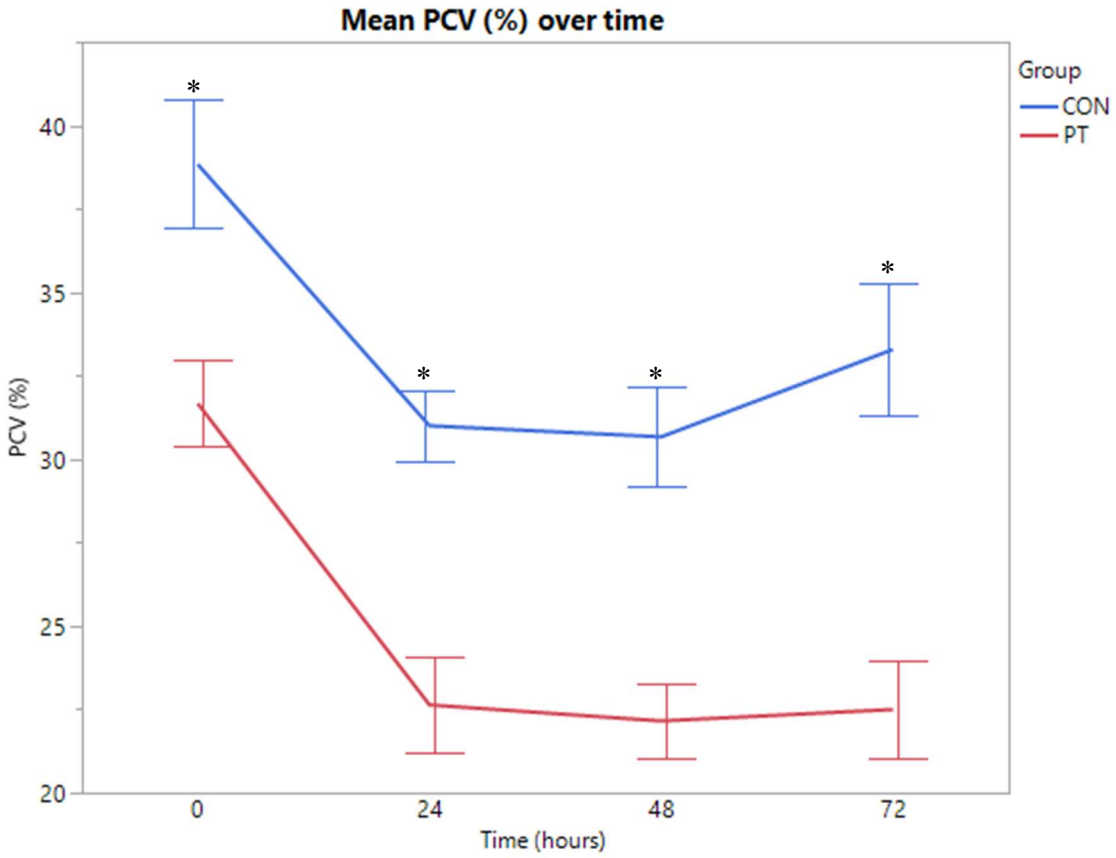

Figure 8: Mean packed cell volume over time for PT versus CON. Each error bar represents 1 standard error from the mean.
** denotes significant difference between groups at that time point ($p<0.05$).*

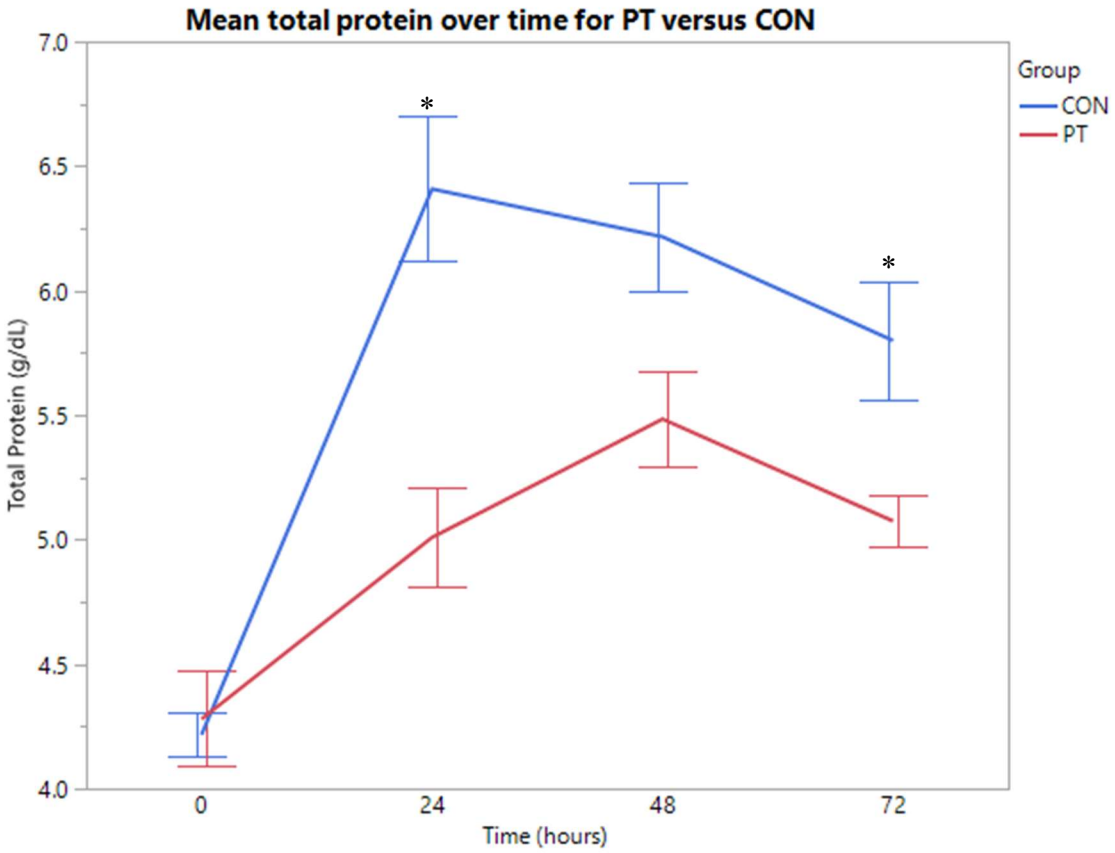

Figure 9: Mean total plasma protein over time for PT versus CON. Each error bar represents 1 standard error from the mean
** denotes significant difference between groups at that time point (p<0.05).*

Weight and Average Daily Gain

There was a significant interaction between time and PT status in the mixed model. There was no significant difference in weights at birth or 24 and 48 hours of age. By 72 hours of age, CON kids had a significantly higher mean weight compared to PT kids (3.95 ± 0.29 kg vs 2.98 ± 0.31 kg, p = 0.0452). In addition, the average daily gain over the first 72 hours was significantly higher in CON kids compared to PT kids with PT actually having a net loss of weight over the first 72 hours (0.082 ± 0.05 kg and -0.12 ± 0.075 kg, respectively, p = 0.0196) (Figure 10).

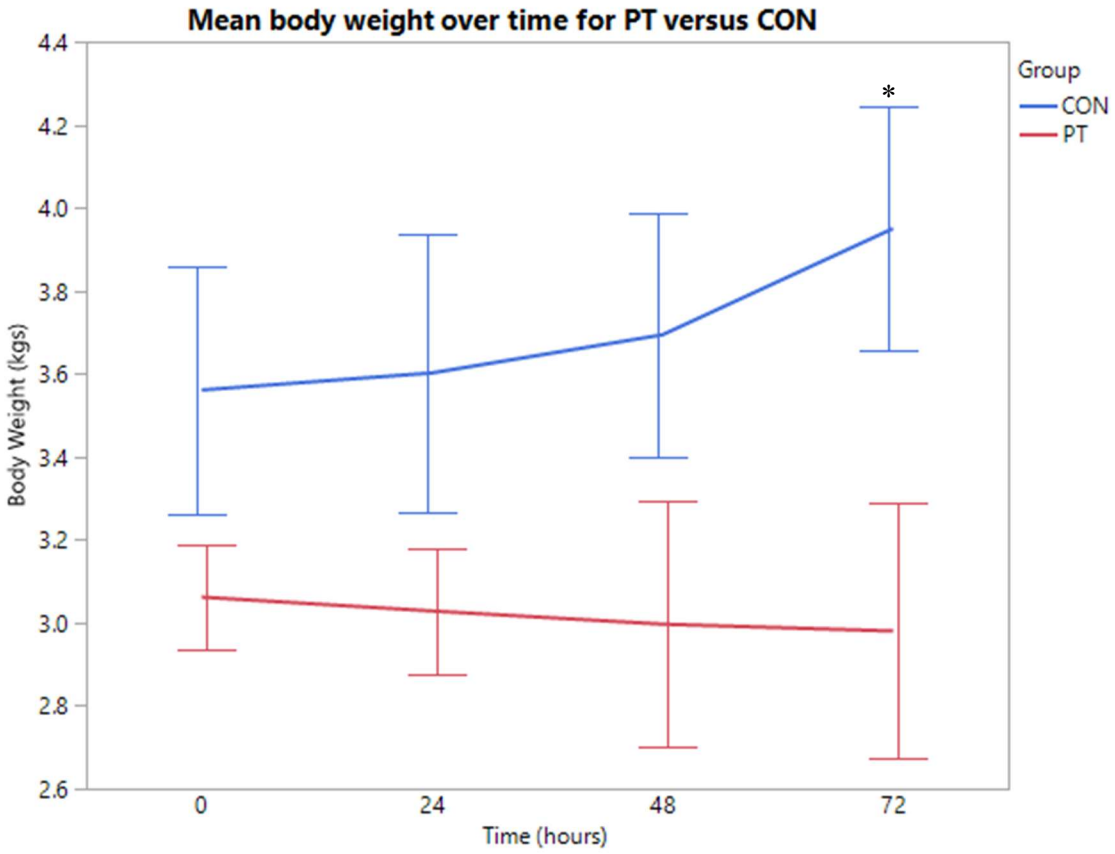

Figure 10: Mean body weight (kgs) over time for PT versus CON. Each error bar represents one standard error from the mean.
** denotes significant difference between groups at that time point (p<0.05).*

Short-term Morbidity and Mortality

CON kids were 1.3 times more likely to survive to discharge than PT kids (95% CI = 1.01,1.77). There was a significant difference in morbidity for the first 12 hours of age. Significantly more PT kids displayed abnormal nursing behavior and weakness shortly after birth compared to CON kids (p = 0.0377). PT kids were 1.45 (95% CI [1.05,2.02]) times more likely to not nurse soon after birth and 1.72 (95% CI [1.04,2.84]) times more likely to exhibit abnormal nursing behavior by 12 hours. More PT kids required tube feedings at 0 and 12 hours of age (p = 0.0053 and 0.0006, respectively) and more CON kids were successfully nursing the dam on their

own at 0 and 12 hours of age (p = 0.0073 and 0.0002). PT kids were 7.7 (95% CI [1.13,52.45] times more likely to need to be tube fed at birth and 2.8 (95% CI [1.39,5.65]) times more likely to need to be tube fed at 12 hours of age. CON kids were 2.92 (95% CI [1.23,6.93]) times more likely to nurse from the dam at birth and 3.5 (95% CI [1.53,8.01]) times more likely to nurse from the dam at 12 hours. There was no significant difference in the number of kids requiring bottle feeding at either 0 or 12 hours of age.

The source for colostrum was significantly different between the PT and CON groups (p=0.0052). All of the CON kids received colostrum sourced solely from the dam. Of the PT kids, 4/16 required colostrum sourced solely from replacer, and 3/16 received a mixture of the dam's colostrum and replacer. This data is summarized in table 4. Kids that received only colostrum replacer were 3.9 (95% CI [1.38-11.23]) times more likely to be classified as failure of passive transfer (total protein < 5.4 g/dL[47]) than kids that received either mixed or dam's colostrum alone. When this was analyzed amongst only the PT kids, there was no significant difference in FPT between kids who received colostrum replacer and those that received only the dam's colostrum (p = 0.238).

	Colostrum Administration			**Colostrum Source**		
	Dam	Bottle	Tube	Dam	Replacer	Mixed
PT	4/16	7/16	9/16	8/15	4/15	3/15
CON	12/12	3/12	0/12	12/12	0/12	0/12

Table 4: Summary of colostrum administration and source for PT and CON groups. Some kids required more than one method of administration. One PT kid died prior to administration of colostrum.

When survivors and non-survivors were compared within the PT group, there were significantly more non-survivors with abnormal nursing behavior and weakness at 0 and 12 hours (p = 0.011 and 0.033, respectively). PT kids with normal nursing behavior were 5 (95% CI

[0.866,28.86]) times more likely to survive to discharge than those that were not exhibiting normal nursing behavior by 12 hours. The following variables were significantly higher in survivors: weight at birth (3.26 ±0.12 vs 2.46 ± 0.08, p <0.0001), blood pH at birth (7.28 ± 0.064 vs 7.18 ± 0.0095, p = 0.0326), PCV at birth (37% ± 0.58 vs 30% ± 1.33, p = 0.0003), blood L-lactate at 12 hours (5.2 ± 0.52 vs 1.9 ± 0.35 mmol/L, p = 0.00007) and blood glucose at 12 hours (117 ± 18.19 vs 32 ± 32 mg/dL, p = 0.0011).

Long-term Morbidity and Mortality

Long-term follow up was available for 12/12 CON kids and 11/16 PT kids. There was a significant difference in long-term survival between CON and PT groups at 3 months (p = 0.0239) with the Kaplan Meier graph between CON and PT shown in figure 9. CON kids were 2.2 (95% CI [1.152,4.20]) times more likely to survive to 3 months than PT kids.

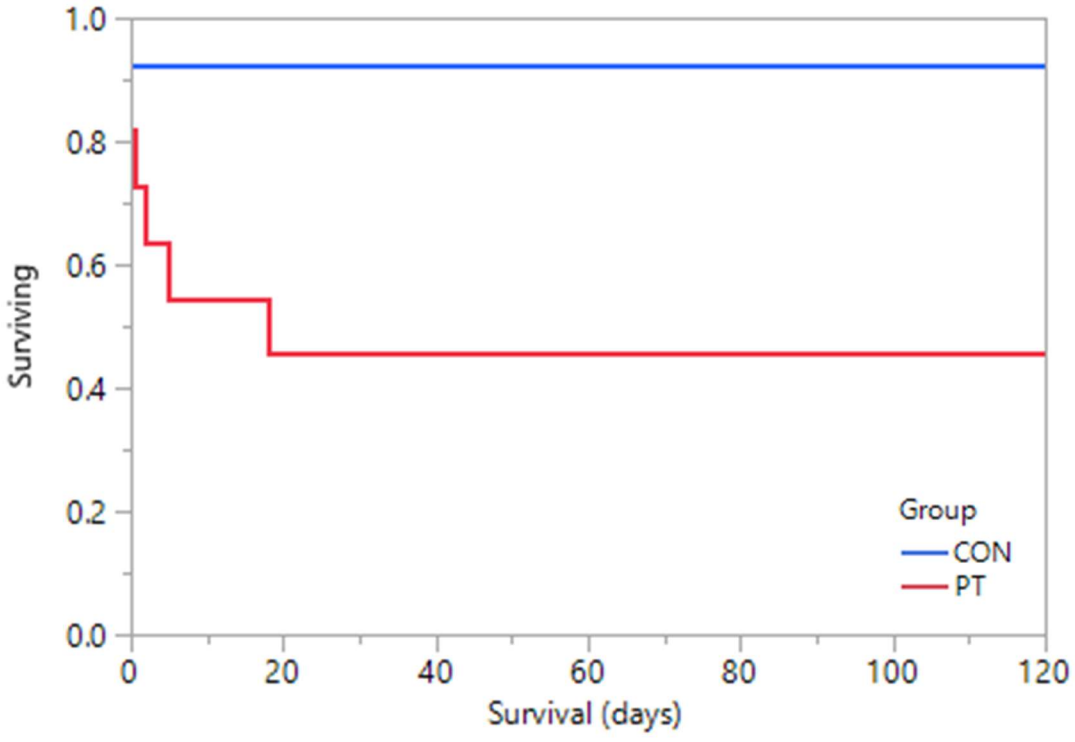

Figure 11: Kaplan-Meier survival graph for PT (red line) versus CON (blue line). Right censored data at 120 days.

When survivors were compared to non-survivors within the PT group, survivors were significantly closer to dam's expected due date at time of birth compared to non-survivors (6.6 ± 0.24 vs 16.33 ± 2.95 days, $p = 0.216$). Significantly fewer survivors required assistance during kidding compared to non-survivors ($p = 0.0105$). PT kids were 4 (95% CI [1.20,13.28]) times more likely to survive if they had unassisted birth than if they required manual traction or delivered by c-section. Additionally, survivors had a significantly higher ADG with a net weight gain of 0.16 ± 0.033 kg compared to the net weight loss of -0.003 ± 0.013 kg for non-survivors ($p = 0.0476$).

CHAPTER V

CONCLUSIONS

The findings of this study show there is an effect of PT on the short- and long-term morbidity and mortality in goat kids. PT affected not only the survival of the kids but also had significant effects on blood L-lactate, blood glucose regulation, and acid-base balance of kids in the first 72 hours of life.

In the peri-partum period, does with PT were more likely to require assistance during parturition than CON does. This corresponds to previous findings of increased incidence of dystocia in ewes with PT[18]. PT kids in this study were more likely to exhibit abnormal nursing behavior and weakness than CON kids, and PT kids that were not nursing by 12 hours had an increased risk of non-survival. Similarly to PT kids in this study, calves that experience dystocia have been shown to be much more likely to be weak, recumbent, and have a poor suckle than calves from normal births[48]. Another study found that perinatal mortality (<12 hours) and general neonatal mortality (12 hours to 45 days) were greater in calves that experienced dystocia[49]. These calves were also shown to be at an increased risk of neonatal disease in the first 45 days of life[49].

The increase in dystocia associated with PT could also help explain the differences seen in arterial blood gas values for this study. Dystocia is associated with prolonged hypoxia and acidosis which favors a continuation of right-to-left vascular shunts[4]. PT kids were significantly more acidemic than CON kids. All kids in this study were sampled within 1 hour of birth after

they were considered stable and breathing well on their own. They were maintained in sternal recumbency as it has been shown that lateral recumbency can reduce the PaO_2 by as much as 30 mmHg[4]. All kids were placed on supplemental oxygen immediately post-partum, this oxygen was removed for at least 5 minutes prior to sampling so as not to falsely increase PaO_2 values[50]. Tharwart, et al[20] found that PT kids were also significantly more acidemic *in utero* when comparing umbilical cord blood with fetuses in non-PT does. The degree of acidemia seen in this study was not as low as seen in the cord blood of PT kids (7.26 ± 0.019 vs 6.94 ± 0.29). This difference could reflect the introduction of alveolar ventilation and less hypoxic extra-uterine environment or a difference in sample types as the cord blood samples were oxygen-poor (venous-like) samples and the current study were arterial samples. However, the CON kids from the current study do not show the same disparity as the *in utero* control measurements performed by Tharwart, et al (7.34 ± 0.023 vs 7.35 ± 0.12). Another possibility for the difference is that the does in Tharwart, et al's study were more severely affected by PT than the current study with likely more significant compromise of placental gas exchange and nutrient transport. The differences seen in BE, HCO_3, and TCO_2 were all consistent with the differences seen between CON and PT kids in the current study. At birth, the PT kids had significantly lower values for those parameters than CON kids, which characterizes a metabolic component to the relative acidosis of PT kids both pre- and post-partum. However, there is not a significant difference seen in the current study between PT and CON for $PaCO_2$ and PaO_2, as was seen in Tharwat et al's study. L-lactate was significantly increased in PT kids in the current study and in the previous *in utero* study[20]. This strong ion is likely to contribute to the metabolic acidosis of PT kids.

Blood L-lactate concentrations are reflective of poor tissue perfusion and tissue oxygenation. It has been shown in foals that venous lactate is normally greater than the adult reference range at birth but decreases over the first 24-48 hours[51]. In the current study, both groups had an elevated mean blood L-lactate at birth and both groups showed a decrease in L-

lactate over the first 48 hours. The PT kids had significantly higher blood L-lactate values up until 24 hours of age. This difference could reflect a poor oxygenation due to hypoventilation in PT kids versus CON kids or a decrease in lactate clearance by the kidney and liver. PT kids were more likely to be premature, which has been suggested to result in higher lactate concentrations in foals[52], however that study only looked at sampling of lactate once, upon admittance to the hospital rather than serially from birth to 72 hours. In sick foals, a decrease in lactate in response to treatment, at 24 hours after hospitalization, correlated to increased survival[51]. Interestingly, in the current study, PT kid non-survivors had a lower blood L-lactate at 12 hours old when compared to survivors. This could possibly reflect over all depletion of glycogen and adipose tissue stores and an increased use of lactate as an energy substrate in non-surviving kids.

Blood glucose values were significantly lower in CON kids compared to PT kids at birth. The relative hyperglycemia in PT kids could reflect a transient insulin-resistance as a result of maternal glucose-insulin imbalance as seen with lambs born to ewes undernourished in late gestation[37] and with human infants born to women with gestational diabetes[40]. Additionally, the increase in blood BHB levels in PT kids immediately post-partum could reflect an increase in the rate of lipolysis. Increased lipolysis would be expected to also increase NEFAs, but there was no significant difference in NEFAs between the two groups in the current study. In a study of maternal feed restriction in late gestation does, male kids born to undernourished dams actually had a decreased NEFA concentration compared to controls, suggesting they mobilized their body reserves less at birth[53]. The increase in BHB at birth may simply reflect the increased maternal BHB. As discussed earlier, foals and calves normally have a blood glucose that is lower than the juvenile reference range immediately post-partum. However, it appears that PT kids were not able to raise their blood glucose to the level of CON kids in the subsequent 72 hours. With the exception of time 0 samples, which were all pre-suckle, there was no standardization of when feeding occurred prior to sampling for blood glucose in the current study. This could explain why

there was such a large variation in blood glucose values collected amongst the kids in the PT group. Most PT kids were being bottle or tube fed for the first 12 hours to ensure adequate passive transfer of immunity. Most CON kids were nursing their dam vigorously and controlling for feeding would have possibly been detrimental to their health.

The respiratory system of PT kids at 72 hours of life does not appear to be as well adapted to extra-uterine life as it is with CON kids. The SO_2 was significantly decreased in PT kids compared to CON kids pointing to a relative hypoxemia and likely hypoventilation. The only arterial blood gas value outside of reference intervals for the PT kids at 72 hours were the SO_2 and PaO_2. SO_2 is a measure of the oxygen saturation of hemoglobin and PaO_2 which reflects how efficiently oxygen can move from the lungs to the blood. The relationship between these two values is not linear, and the decline seen with the PT kids at 72 hours is predictable using the oxygen-hemoglobin dissociation curve where a PaO_2 of 60 mmHg and SO_2 of 90% represents the shoulder of the curve. This would suggest that the decrease in both values has to do with an inefficient transfer of oxygen from the alveoli to the blood. This could be from a structural or functional immaturity of the lung, surfactant deficiency, acute lung injury (respiratory distress syndrome), atelectasis of the lung, or altered pulmonary vascular reactivity. Most likely, this points to a relative immaturity in lung function between PT and CON kids or a tendency for PT kids to be recumbent and have more atelectic lung. A similar pattern of hypoxemia can occur with continued right-to-left shunting of blood, however we would expect to see cyanosis and marked dyspnea in such patients. The increases in BE, HCO_3, and TCO_2 compared to CON kids at 72 hours indicate that the relative hypercapnia of PT kids is of a chronic nature. This could explain why they had a significantly higher pH at 72 hours despite the fact that PT kids were significantly more acidemic at birth compared to CON kids.

The PCV of PT kids were significantly lower compared to CON kids throughout the study. Kids in both groups showed a decrease in PCV throughout the study period, which may be

attributable to blood loss for sampling purposes. This seems unlikely, as cumulative sample volume was approximately 13 ml from each kid. When presented as a percent of blood volume for the average weight of each group the amount of blood drawn at 72 hours represents <1% in each group (0.73% in the PT group and 0.55% in the CON group). This amount of blood loss is unlikely to cause an appreciable affect on the PCV. Furthermore, the difference between the two groups occurs prior to any blood samples being taken, and the two groups show a similar trend in their PCV values over time in figure 6. The dam had a significant statistical effect on PCV in the multiple measures model and it is likely that PT dams were simply more anemic than CON dams. The average PCV of the PT dams in this study, based on their medical records from admission, was 22.8% but there were inconsistent records on whether these measurements were falsely elevated based on hydration. There was no blood work performed on the CON dams to determine whether or not they were anemic at parturition. The pathologic link of PT and parasitism would support the claim that PT dams have a lower PCV[3]. This decrease in PCV likely contributed to hypoxia in PT kids by decreasing the oxygen carrying capacity in the blood, but hypoxia should result in polycythemia rather than anemia in the kids. PT might have a role in decreased production of red blood cells, and perhaps other cell lines are involved although this was not looked at in the current study or noted in previous literature. Decreased PCV in PT kids was associated with an increased risk of non-survival.

TP was also significantly lower in PT kids than CON kids after 24 hours. A previously published cut off for goat serum total protein via refractometry found that 5.4 g/dL correlated to a serum immunoglobulin level of 12 g/dL which is indicative of adequate passive transfer at 48 hours of age[47]. Although there was no difference in the rate of failure of passive transfer between groups, PT kids did show a decrease in TP at 24 and 72 hours. Studies of passive transfer in calves have found that regardless of the cut-off for passive transfer, a higher total protein correlates with more positive health and performance outcomes later in life.[54-56] In this study, kids

were either tube fed or bottle fed 10% of their body weight with the dam's colostrum or colostrum replacer as to avoid failure of passive transfer. All of CON kids received colostrum from their dam, either by direct nursing or through bottle or tube feeding. Colostrum replacer was given when the dam failed to produce enough milk for her kids. Parity can affect the quality and quantity of colostrum made by the dam, however in this study all does were multiparous.[57,58] It is likely that the lack of colostrum production is related to the PT status of the doe. PT has also been correlated to a decrease in milk and colostrum production by the dam.[18,59] The PT kids in this study were more likely to receive colostrum replacer, with 3/15 receiving a mixture of colostrum replacer and the dam's colostrum and 4/15 only receiving the replacer. There was no significant difference in FPT for PT kids receiving either colostrum replacer or the dam's colostrum. One study showed that total protein measurements by refractometry did not accurately assess IgG levels in calves being fed either colostrum substitutes or replacers.[60] PT kids were at an increased risk of abnormal nursing behavior and more frequently needed to be tube fed versus nursing a bottle or nursing off the dam. Had this intervention not been performed the failure of passive transfer rate would have likely been increased in PT kids versus CON kids. The lower plasma TP could reflect a lower efficiency of absorption of immunoglobulins due to acidemia and tube-feeding. In calves, studies have shown that hypoxia, acidosis, and tube-feeding can have a variable but sometimes negative effect on timing and efficiency of absorption of immunoglobulins.[61-63] A lack of colostrum production by PT dams increases the likelihood that PT kids needed colostrum replacer, which may not be as efficient a source of immunoglobulins as compared to natural colostrum.

In the current study, there was no significant difference between weights of PT and CON kids until 72 hours. This could be due to the fact that most of the CON does were carrying twins and triplets, and only one CON doe had a singleton. We would expect the birthweights to decrease with an increased number of kids per doe. PT kids were much more likely to lose weight

over the first 72 hours of life, and this was also seen to be associated with non-survival at 3 months of age. In a study of late- term feed restriction in goats, kids born to undernourished dams had a smaller abdominal girth, body mass index, and density index when compared to control kids. Male kids had a smaller birthweight but no significant differences were seen for weight or morphometric measurements thereafter.[53]

Short- and long-term morbidity and mortality was significantly greater for PT kids compared to CON kids in the current study. Increased short-term morbidity was characterized by an increased risk of abnormal nursing behavior and weakness and an increased risk of needing to be tube-fed. Short-term non-survival was associated with lower birthweights, more severe acidemia at birth, lower PCV, and lower blood L-lactate and blood glucose levels at 12 hours of age. Premature kids were not at an increased risk of short-term mortality but were at an increased risk of non-survival to 3 months. Although there was a significant loss of follow up for PT kids (5/16), it was still shown that dystocia and a net weight loss in the first 72 hours were risk factors for non-survival to 3 months.

In summary, the current study has shown that PT creates several risk factors for unthrifty kids with an increase in difficult births, increased risk of abnormal nursing and weakness, and a decrease in cardiopulmonary efficiency. There may also be some effect on insulin-glucose regulation, warranting further investigation. The sample size in the current study was rather small. There was significant variation in the severity of disease in the PT does of the current study and there was no way to control for different treatments, such as induction of parturition or dextrose and insulin infusions, and their potential effects on these results. Despite these limitations, several important conclusions were seen. Overall, this study shows that the difference in PT kids compared to CON kids to be attributed to altered respiratory function and poor energy reserves and energy mobilization in the peri-partum period. Most abnormalities in blood L-lactate, blood glucose, and arterial blood gases were resolved by 48-72 hours, but PT kids remained inferior in

their ventilatory capabilities by 72 hours. Clinically, PT kids may benefit from prolonged oxygen supplementation, even if they do not show signs of dyspnea. Additionally, these kids require more rigorous monitoring and intervention for abnormal nursing behavior and weight loss via bottle or tube feedings. More research comparing PT kids and CON kids born as a result of dystocia should be performed to eliminate dystocia as a confounding variable.

REFERENCES

1. Simpson KM, Taylor JD, Streeter RN. Evaluation of prognostic indicators for goats with pregnancy toxemia. Journal of the American Veterinary Medical Association 2019;254:859-867.
2. Vasava PR, Jani RG, Goswami HV, et al. Studies on clinical signs and biochemical alteration in pregnancy toxemic goats. Veterinary World 2016;9:869-874.
3. Barbagianni MS, Giannenas E, Papadopoulos E, et al. Pregnancy toxaemia in ewes: development of an experimental model and potential interactions with gastrointestinal nematode infections. Small Ruminant Research 2015;133:102-107.
4. Large animal internal medicine. 4th ed.. ed. St. Louis, Mo.: St. Louis, Mo. : Mosby Elsevier, 2009.
5. Szenci O. Role of acid-base disturbances in perinatal mortality of calves. Acta Vet Hung 1985;33:205-220.
6. Adams R, Holland MD, Aldridge B, et al. Arterial blood sample collection from the newborn calf. Veterinary Research Communications 1991;15:387-394.
7. Rose RJ, Rossdale PD, Leadon DP. Blood gas and acid--base status in spontaneously delivered, term-induced and induced premature foals. J Reprod Fertil Suppl 1982;32:521-528.
8. Fowden AL, Ward JW, Wooding FPB, et al. Programming placental nutrient transport capacity. The Journal of Physiology 2006;572:5-15.
9. Gustafsson JJIJMR. Neonatal energy substrate production. 2009;130:618-623.
10. Kasari TR. Physiologic mechanisms of adaptation in the fetal calf at birth. Vet Clin North Am Food Anim Pract 1994;10:127-136.
11. Axon JE, Palmer JE. Clinical pathology of the foal. Vet Clin North Am Equine Pract 2008;24:357-385, vii.
12. Ogata ESJPCoNA. Carbohydrate metabolism in the fetus and neonate and altered neonatal glucoregulation. 1986;33:25-45.

13. Girard JJN. Gluconeogenesis in late fetal and early neonatal life. 1986;50:237-258.
14. Bougneres P-F, Rocchiccioli F, Nurjhan N, et al. Stable isotope determination of plasma lactate conversion into glucose in fasting infants. 1995;268:E652-E659.
15. Marcus C, Ehren H, Bolme P, et al. Regulation of lipolysis during the neonatal period. Importance of thyrotropin. 1988;82:1793-1797.
16. Bougneres P, Lemmel C, Ferre P, et al. Ketone body transport in the human neonate and infant. 1986;77:42-48.
17. Kalhan SC, Iben SJCip. PROTEIN METABOLISM IN THE EXTREMELY LOW–BIRTH WEIGHT INFANT. 2000;27:23-56.
18. Barbagianni MS, Spanos SA, Ioannidi KS, et al. Increased incidence of peri-parturient problems in ewes with pregnancy toxaemia. Small Ruminant Research 2015;132:111-114.
19. Sakha M. Metabolic adaptation after experimental clinical pregnancy toxemia in ewes. Comparative Clinical Pathology 2016;25:649-653.
20. Tharwat M, Al-Sobayil F. Cord and jugular blood acid–base and electrolyte status and haematobiochemical profiles in goats with naturally occurring pregnancy toxaemia. Small Ruminant Research 2014;117:73-77.
21. Lima MS, Silveira JM, Carolino N, et al. Usefulness of clinical observations and blood chemistry values for predicting clinical outcomes in dairy goats with pregnancy toxaemia. Irish Veterinary Journal 2016;69:(24 October 2016).
22. Balikci E, Yildiz A, Gurdogan F. Investigation on some biochemical and clinical parameters for pregnancy toxemia in Akkaraman ewes. Journal of Animal and Veterinary Advances 2009;8:1268-1273.
23. Schlumbohm C, Harmeyer J. Twin-pregnancy increases susceptibility of ewes to hypoglycaemic stress and pregnancy toxaemia. Research in Veterinary Science 2008;84:286-299.
24. Lima MS, Pascoal RA, Stilwell GT. Glycemia as a sign of the viability of the foetuses in the last days of gestation in dairy goats with pregnancy toxaemia. Irish Veterinary Journal 2012;65:(23 January 2012).
25. Hay Jr WW, Sparks JW, Wilkening RB, et al. Partition of maternal glucose production between conceptus and maternal tissues in sheep. 1983;245:E347-E350.
26. Fowden AL, Mundy L, the late Silver MJTJop. Developmental regulation of glucogenesis in the sheep fetus during late gestation. 1998;508:937-947.
27. Carver TD, Hay Jr WWJAJoP-E, Metabolism. Uteroplacental carbon substrate metabolism and O2 consumption after long-term hypoglycemia in pregnant sheep. 1995;269:E299-E308.
28. Kasimanickam RK. Subclinical Pregnancy Toxemia-Induced Gene Expression Changes in Ovine Placenta and Uterus. 2016;3.
29. Han HC, Austin KJ, Nathanielsz PW, et al. Maternal nutrient restriction alters gene expression in the ovine fetal heart. Journal of Physiology 2004;558:111-121.

30. Bubb KJ, Cock ML, Black MJ, et al. Intrauterine growth restriction delays cardiomyocyte maturation and alters coronary artery function in the fetal sheep. Journal of Physiology 2007;578:871-881.
31. Lipsett J, Tamblyn M, Madigan K, et al. Restricted fetal growth and lung development: A morphometric analysis of pulmonary structure. Pediatric Pulmonology 2006;41:1138-1145.
32. Dumortier O, Blondeau B, Duvillié B, et al. Different mechanisms operating during different critical time-windows reduce rat fetal beta cell mass due to a maternal low-protein or low-energy diet. Diabetologia 2007;50:2495-2503.
33. Gao F, Liu Y, Li L, et al. Effects of maternal undernutrition during late pregnancy on the development and function of ovine fetal liver. Animal Reproduction Science 2014.
34. Duehlmeier R, Fluegge I, Schwert B, et al. Insulin Sensitivity during Late Gestation in Ewes Affected by Pregnancy Toxemia and in Ewes with High and Low Susceptibility to this Disorder. Journal of Veterinary Internal Medicine 2013;27:359-366.
35. Lima MS, Cota JB, Vaz YM, et al. Glucose intolerance in dairy goats with pregnancy toxemia: lack of correlation between blood pH and beta hydroxybutyric acid values. Canadian Veterinary Journal 2016;57:635-640.
36. Long NM, Prado-Cooper MJ, Krehbiel CR, et al. Effects of nutrient restriction of bovine dams during early gestation on postnatal growth and regulation of plasma glucose. J Anim Sci 2010;88:3262-3268.
37. Kongsted AH, Tygesen MP, Husted SV, et al. Programming of glucose–insulin homoeostasis: long-term consequences of pre-natal versus early post-natal nutrition insults. Evidence from a sheep model. Acta Physiologica 2014;210:84-98.
38. Mericq V, Ong K, Bazaes R, et al. Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small-and appropriate-for-gestational-age children. 2005;48:2609-2614.
39. Diderholm B, Ewald U, Ahlsson F, et al. Energy substrate production in infants born small for gestational age. 2007;96:29-34.
40. Sunehag A, Gustafsson J, Ewald UJPr. Very immature infants (≤ 30 wk) respond to glucose infusion with incomplete suppression of glucose production. 1994;36:550.
41. Li B, Concepcion K, Meng X, et al. Brain-immune interactions in perinatal hypoxic-ischemic brain injury. Prog Neurobiol 2017;159:50-68.
42. Tennent-Brown BS, Morrice AV, Reed S. The Equine Neonatal Central Nervous System: Development and Diseases. Veterinary Clinics of North America: Equine Practice 2015;31:587-600.
43. Furr MJTCoceftpv. Perinatal asphyxia in foals. 1996.
44. Vaala W. Peripartum asphyxia syndrome in foals. PROCEEDINGS-UNIVERSITY OF SYDNEY POST GRADUATE FOUNDATION IN VETERINARY SCIENCE 1996;109-126.
45. Galvin N, Collins D. Perinatal asphyxia syndrome in the foal: review and a case report. Irish Veterinary Journal 2004;57:707.

46. Doré V, Dubuc J, Bélanger A, et al. Evaluation of the accuracy of an electronic on-farm test to quantify blood β-hydroxybutyrate concentration in dairy goats. Journal of dairy science 2013;96:4505-4507.
47. O'Brien JP, Sherman DM. Field methods for estimating serum immunoglobulin concentrations in newborn kids. Small Ruminant Research 1993;11:79-84.
48. Bendali F, Sanaa M, Bichet H, et al. Risk factors associated with diarrhoea in newborn calves. Vet Res 1999;30:509-522.
49. Wittum TE, Salman MD, King ME, et al. Individual animal and maternal risk factors for morbidity and mortality of neonatal beef calves in Colorado, USA. Preventive Veterinary Medicine 1994;19:1-13.
50. Rose RJ, Hodgson DR, Leadon DP, et al. Effect of intranasal oxygen administration on arterial blood gas and acid base parameters in spontaneously delivered, term induced and induced premature foals. Res Vet Sci 1983;34:159-162.
51. Castagnetti C, Pirrone A, Mariella J, et al. Venous blood lactate evaluation in equine neonatal intensive care. Theriogenology 2010;73:343-357.
52. Borchers A, Wilkins PA, Marsh PM, et al. Association of admission L-lactate concentration in hospitalised equine neonates with presenting complaint, periparturient events, clinical diagnosis and outcome: a prospective multicentre study. Equine Veterinary Journal 2012;44:57-63.
53. Laporte-Broux B, Roussel S, Ponter AA, et al. Short-term effects of maternal feed restriction during pregnancy on goat kid morphology, metabolism, and behavior1. Journal of Animal Science 2011;89:2154-2163.
54. Dewell RD, Hungerford LL, Keen JE, et al. Association of neonatal serum immunoglobulin G1 concentration with health and performance in beef calves. J Am Vet Med Assoc 2006;228:914-921.
55. Donovan GA, Dohoo IR, Montgomery DM, et al. Associations between passive immunity and morbidity and mortality in dairy heifers in Florida, USA. Prev Vet Med 1998;34:31-46.
56. Tyler JW, Hancock DD, Wiksie SE, et al. Use of serum protein concentration to predict mortality in mixed-source dairy replacement heifers. J Vet Intern Med 1998;12:79-83.
57. Furman-Fratczak K, Rzasa A, Stefaniak T. The influence of colostral immunoglobulin concentration in heifer calves' serum on their health and growth. J Dairy Sci 2011;94:5536-5543.
58. Kehoe S, Heinrichs AJ, Moody M, et al. Comparison of immunoglobulin G concentrations in primiparous and multiparous bovine colostrum. The Professional animal scientist 2011;27:176-180.
59. Barbagianni MS, Mavrogianni VS, Katsafadou AI, et al. Pregnancy toxaemia as predisposing factor for development of mastitis in sheep during the immediately post-partum period. Small Ruminant Research 2015;130:246-251.
60. Quigley JD, 3rd, Kost CJ, Wolfe TM. Absorption of protein and IgG in calves fed a colostrum supplement or replacer. J Dairy Sci 2002;85:1243-1248.

61. Drewry JJ, Quigley JD, 3rd, Geiser DR, et al. Effect of high arterial carbon dioxide tension on efficiency of immunoglobulin G absorption in calves. Am J Vet Res 1999;60:609-614.

62. Hopkins BA, Quigley JD, 3rd. Effects of method of colostrum feeding and colostrum supplementation on concentrations of immunoglobulin G in the serum of neonatal calves. J Dairy Sci 1997;80:979-983.

63. Tyler H, Ramsey H. Hypoxia in neonatal calves: effect on intestinal transport of immunoglobulins. J Dairy Sci 1991;74:1953-1956.

VITA

Leslie Frances Wagner

Candidate for the Degree of

Master of Science

Thesis: CHARACTERIZATION OF SHORT- AND LONG-TERM MORBIDITY AND MORTALITY OF GOAT KIDS BORN TO DOES WITH PREGNANCY TOXEMIA

Major Field: Veterinary Biomedical Sciences

Biographical:

Education:

Completed the requirements for the Master of Science in your Veterinary Biomedical Sciences at Oklahoma State University, Stillwater, Oklahoma in December, 2019.

Completed the requirements for the Doctor of Veterinary Medicine at Texas A&M University, College Station, TX in 2015

Completed the requirements for the Bachelor of Science in Biomedical Science at Texas A&M University, College Station, TX in 2011.

Experience:

Internship in Food Animal Medicine and Surgery at Oklahoma State University 2015-2016.

ACVIM residency in Food Animal Medicine and Surgery at Oklahoma State University from 2016-2019.

Clinical assistant professor of livestock services at Kansas State University from August 2019-present.

Professional Memberships:

American College of Veterinary Internal Medicine

American Association of Bovine Practitioners