STANDARD ARTICLE

Journal of Veterinary Internal Medicine ACVIM

Open Access

American College of Veterinary Internal Medicine

Characterization of short- and long-term morbidity and mortality of goat kids born to does with pregnancy toxemia

Leslie F. Weaver[1] 🟢 | Melanie J. Boileau[2] 🟢 | Lyndi L. Gilliam[2] | Jared D. Taylor[3]

[1]Veterinary Clinical Sciences, Kansas State University, Manhattan, Kansas

[2]Veterinary Clinical Sciences, Oklahoma State University, Stillwater, Oklahoma

[3]Veterinary Pathobiology, Oklahoma State University, Stillwater, Oklahoma

Correspondence
Leslie F. Weaver, 1800 Denison Avenue, Manhattan, KS 66502.
Email: lfweaver@vet.k-state.edu

Abstract

Background: Pregnancy toxemia is a common metabolic disease of periparturient small ruminants. Information on its effects on metabolism and perinatal adaptation of newborn lambs and kids is lacking.

Objectives: Evaluate differences in morbidity, mortality, and common biochemical and hematologic variables between pregnancy toxemia kids (PT) and control kids (CON).

Animals: Sixteen kids born to does being treated at the hospital for pregnancy toxemia (blood beta-hydroxybutyrate concentration [BHB] > 1.2 mmol/L) and 12 kids from healthy dams (dam BHB < 1.2 mmol/L) that kidded at the hospital.

Methods: In this cohort study, serial measurements of blood L-lactate, glucose, and BHB concentrations, arterial blood gases, hematocrit, total protein concentrations, nonesterified fatty acids (NEFAs) concentrations, and body weight were compared between groups over the first 72 hours of life. Long-term follow-up was performed after 3 months.

Results: Pregnancy toxemia kids were more likely to require tube feeding at 0 and 12 hours (relative risk 7.7 [1.13, 52.45] and 2.8 [1.39, 5.65]). Pregnancy toxemia kids were more acidemic (7.26 ± 0.069 vs 7.34 ± 0.079, P = .003) and hyperlactatemic (8.17 ± 2.57 vs 5.48 ± 2.71, P = .003) at birth than CON kids. Control kids were 1.1 [1.01, 1.77] times more likely to survive to discharge and 2.2 [1.15, 4.20] times more likely to survive to 3 months than PT kids.

Conclusions and Clinical Importance: Pregnancy toxemia kids had higher short- and long-term mortality and were more likely to require perinatal intervention. Weight loss in the first few days could be a useful predictor of nonsurvival.

KEYWORDS
acidemia, blood gas, glucose, lactate, metabolic, neonate, respiration, small ruminant

1 | INTRODUCTION

Pregnancy toxemia (PT) is an important metabolic disease affecting sheep and goats, whether meat, dairy, or fiber breeds. Pregnancy toxemia occurs in the last trimester with highest incidence in the last

14 days, when energy demand for fetal growth is at its peak. It is seen most commonly in multiparous does carrying multiple fetuses.[1] Undernutrition and altered energy metabolism play important roles in the dam with PT, but less is known about its effects on the energy metabolism of the offspring. The placenta utilizes 50% to 70% of the glucose and oxygen delivered to the uterus and transfers the remainder to the fetal tissues.[2] In subclinical PT ewes, gene expression responsible for vascularization in the uterus and placenta was decreased, and expression of genes that respond to placental hypoxia were increased.[3] These hemodynamic changes affect the rate of transplacental nutrient exchange and retard fetal growth. The enzymes for gluconeogenesis are present early in fetal development, but the fetus will only produce its own glucose under extreme conditions such as maternal starvation.[4] Lambs born to ewes fed 50% of energy and protein requirements during late gestation had permanently decreased insulin sensitivity. Although the ewes in this study did not have clinical PT, results suggested that prenatal undernutrition can influence metabolic processes of the offspring later in life.[5] Ewes with PT, or at high risk for PT, have been shown to have relative insulin resistance, higher baseline lipolysis, and impaired insulin : glucagon ratios.[6] Dairy goats with PT had marked glucose intolerance after an oral glucose challenge when compared to high-producing pregnant and nonpregnant does.[7] In studies of pregnant women with gestational diabetes, infants were shown to have altered glucose regulation.[4] To date, no research has been done to show this relationship between PT dams and the metabolism of their offspring.

Morbidity and mortality in PT offspring rarely are reported. One study described an increase in perinatal mortality for PT lambs compared to control lambs.[8] When outcomes of PT were studied in dairy goats, a high dam case fatality was found, and an increase in kid survival was observed if induction of parturition or cesarean section was performed.[9]

Our objectives were to determine the morbidity and mortality of goat kids associated with PT in both the short and long term. A secondary objective was to measure key biochemical variables reflective of energy metabolism and neonatal adjustment to extra-uterine life (eg, blood glucose, beta-hydroxybutyrate [BHB], L-lactate, and non-esterified fatty acid [NEFA] concentrations and arterial blood gases) within the first 3 days after birth.

2 | MATERIALS AND METHODS

All protocols and procedures were approved by the Institutional Animal Care and Use Committee at Oklahoma State University. Owners gave permission for their animals to be enrolled by either signing a consent form or verbal communication by phone.

2.1 | Animal selection

This prospective cohort study was performed using kids born to does with clinical PT (defined as a blood BHB concentration > 1.2 mg/dL)

being treated at the Oklahoma State University teaching hospital in Stillwater, Oklahoma. Control (CON) kids were from healthy, multiparous late pregnant does, defined by blood BHB concentration < 1.2 mg/dL and normal physical examination findings. Control does were provided by 2 different farms and admitted for kidding watch 1 to 2 days before their expected due dates based on observed breeding or laparoscopic artificial insemination dates. All does had blood BHB concentrations measured at presentation using a point-of-care analyzer previously validated for goats (Precision Xtra, Abbott Diabetes Care).[10] Pregnancy toxemia kids were enrolled from January 2018 through November 2018 and CON kids were enrolled from October 2018 through May 2019. All parturition events for PT and CON does occurred at the teaching hospital and were attended by at least 1 of the investigators (M.J. Boileau, L.F. Weaver). Parturition was characterized as a normal vaginal delivery (no assistance needed), assisted vaginal delivery (≥1 kids required manual traction for delivery), or cesarean section. 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 immediately after parturition. 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, sex, total number of live kids delivered, and numbers of kids born alive, stillborn, or with birth defects all were recorded for each parturition event. Historical and clinical data collected for PT does included expected due date, clinical signs on presentation, and treatments administered before presentation or while hospitalized.

2.2 | Sample collection and analysis

Immediately after birth, all kids were maintained in sternal recumbency and received neonatal resuscitation including towel drying, suction of the airway, and oxygen delivered at 5 L/min via a pediatric intranasal cannula until they were breathing autonomously. All kids were stable within an hour of birth, and neonatal resuscitation was discontinued at least 5 minutes before the first sample collection (0 hour). 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 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, New York). Arterial blood was collected at time 0 and 72 hours from the median artery using a 1 mL heparinized arterial blood gas collection kit (Carefusion) while the kid was restrained in an upright position. The arterial blood sample 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. Blood BHB was analyzed using a point-of-care meter (Precision Xtra, Abbott Diabetes Care).[10] Packed cell volume (PCV) was measured in a microhematocrit tube using blood from the EDTA tube centrifuged at 9500 rpm for 7 minutes. The plasma total protein concentration (TP) was measured by optical refractometry. Packed cell volume and TP were determined at times 0, 24, 48, and 72 hours. Failure of passive transfer was defined as TP < 5.4 g/dL at 48 hours of age.[11] Weights for each kid were determined at times 0, 24, 48, and 72 hours using an electronic scale. Clinicians were blinded to the results of blood constituents included in the study.

2.3 | Morbidity and mortality

Goat kids were monitored each hour for nursing activity. If colostrum was unavailable from the dam, a commercial bovine immunoglobulin colostrum replacer effective for passive transfer of immunity in lambs[12] (Calf's Choice Total HiCal, Alta Genetics, Inc) was given by bottle (if the kid voluntarily consumed colostrum) or orogastric intubation (if no suckle was present) at 10% body weight over the first 12 hours. At times 0 and 12 hours, it was recorded whether colostrum was nursed from the dam, tube fed, or bottle fed. The source of colostrum was recorded as either all from the dam, mixed, or solely colostrum replacer. Colostrum quality of the dam was not assessed. Nursing behavior was evaluated by 1 of the investigators (L.F. Weaver) and recorded at times 0 and 12 hours. Abnormal nursing behavior was defined as 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. Short-term morbidity and mortality were evaluated at times 0, 12, 24, 48, and 72 hours. Short-term morbidity was defined by 3 categories: normal (independently active and nursing well), moderate (weak suckle, assistance needed to nurse), or severe (unable to stand, no suckle, tube feeding required). 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 were determined by phone conversations with the owners when the kids were 3 months of age. Long-term morbidity was defined as either fulfillment of the animal's purpose (kept or sold as a breeding or exhibition animal), early death, or culling because of poor performance.

2.4 | Statistical methods

Power calculations were performed with the following assumptions: α = 0.05, ratio of approximately 1 control kid for each kid born to a PT doe; β of 0.2 (power of 80%). The number of enrollees provided a >90% probability of detecting significant differences of 0.1 unit of measurement in blood pH, base excess, and arterial partial pressure of carbon dioxide ($PaCO_2$) (assuming SDs within each population of 0.1 for each parameter). All data were analyzed using JMP Pro 14

(SAS Institute, Inc, Cary, North Carolina). All descriptive statistics were reported as mean ± SD. All continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data were analyzed using a t test. Nonparametric continuous data were analyzed using the Wilcoxon rank sum exact test. Categorical variables were analyzed using a Fisher's exact test. Relative risks were calculated whenever 2 levels of categorical data were available and were recorded with 95% confidence intervals (CIs). Comparisons were made for all variables between PT kids and CON kids. Kaplan-Meier plots, with right-censored data, were used to identify differences in survival between groups. All variables were compared between surviving and nonsurviving PT 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 2- and 3-way interactions as fixed effects and individual kid and dam as random effects. If an interaction was identified, the repeated measures were evaluated separately using either the Student's t test or Wilcoxon rank sum exact test with a Holm-Bonferroni correction for multiple comparisons. Values of $P < .05$ were considered significant.

3 | RESULTS

3.1 | Dam BHB status and parturition factors

Sixteen kids were enrolled from 6 does with clinical PT, and 12 kids from 6 CON does. Pregnancy toxemia does were from 4 different farms and 2 PT does came from the same farm as 3 CON does. The other CON does came from a different farm, but 1 that had experienced PT cases in the past. All PT and CON does were multiparous. All does and kids were Boer, and no significant difference was found between the distribution of male (9/16 PT and 5/12 CON) and female (7/16 PT and 7/12 CON) kids between the 2 groups ($P = .7$). Parturition was induced by IM injections of 10 mg dexamethasone and 10 mg dinoprost tromethamine in 4/6 PT does and 0/6 CON does. One doe was induced in the hospital because of worsening condition. Three does were induced by the owner before presentation because of PT and proximity to expected due date. Before presentation, 4/6 does had been treated PO with propylene glycol by the owner. All PT does presented with swollen limbs, anorexia, and lethargy. None of the PT does were recumbent on presentation or during hospitalization. During hospitalization, PT does received IV infusions of dextrose (6/6), IV bicarbonate (2/6), nonsteroidal anti-inflammatory drugs (6/6), PO propylene glycol (2/6), transfaunation (6/6), and antibiotics (ceftiofur sodium, 5/6; florfenicol, 3/6). The median presenting temperature for PT does was 103.1°F (range, 102.8°F-104.3°F). The median presenting respiratory rate for PT does was 84 breaths per minute (range, 36-115 breaths per minute). Due dates were based on observed breedings in 3/6 PT does and 3/6 CON does and laparoscopic artificial insemination in 3/6 PT does and 3/6 CON does. Pregnancy toxemia does have significantly higher presenting blood BHB concentrations than CON does (4.44 ± 1.36 vs 0.6 ± 0.031 mmol/L,

P < .001). No significant difference was found in either total number of live or stillborn kids per parturition event, and none of the kids in the study had congenital defects. The mean days before due date for the PT doe was 8.81 ± 7.56 days (range, 2-21 days). Pregnancy toxemia doe also had a numerically higher, but not statistically different, frequency of assisted delivery and cesarean section compared to CON does (*P* = .15). Table 1 summarizes these parturition variables for both PT and CON groups.

3.2 | Blood lactate

L-lactate concentrations were significantly higher in PT kids compared with CON kids at sampling times 0 and 12 hours (*P* = .02 and .01, respectively). Mean ± SD lactate concentrations for both groups of kids are presented in Figure 1.

3.3 | Blood glucose

A significant difference was found between PT and CON groups at sampling times 24 and 72 hours (*P* = .04 and .01, respectively). Mean ± SD for blood glucose concentration are presented in Figure 2.

3.4 | Kid beta-hydroxybutyrate

The only time point at which blood BHB differed between the 2 groups of kids was time 0 when PT BHB was significantly higher than CON BHB (0.93 ± 0.116 mmol/L vs 0.008 ± 0.029 mmol/L, *P* = .02; Figure 3).

TABLE 1 Parturition variables for PT and CON groups

	PT	CON
Doe BHB (mmol/L)	4.44 (1.9-6.2)	0.6 (0.2-1)
Days hospitalized before parturition	4.5 (0-15)	2.17 (0-4)
Days premature	8.81 (2-21)	—
Induced	4/6	0/6
Unassisted delivery	3/6	4/6
Assisted delivery	0/6	2/6
Cesarean section	3/6	0/6
Number of kids per doe	2.88 (2-4)	2.58 (1-3)
Number of stillborn	1/17	1/13
Number of FPT kids	5/13[a]	2/12
Doe fatality	1/6	0/6

Note: Continuous data expressed as mean and range (in parentheses). Categorical data expressed as proportions.
Abbreviations: BHB, beta-hydroxybutyrate concentration; CON, control; FPT, failure of passive transfer; PT, pregnancy toxemia.
[a]Three kids died before failure of passive transfer could be evaluated at 48 hours.

3.5 | Nonesterified fatty acids

No significant difference was found between NEFA measured at birth in PT (0.318 ± 0.21 mEq/L) and CON (0.328 ± 0.267 mEq/L) groups (*P* = .32).

3.6 | Arterial blood gases

The partial pressures of carbon dioxide ($PaCO_2$) and oxygen (PaO_2) decreased over time, but no significant effect of PT status was found for either variable. Oxygen saturation (SO_2) increased over time in both groups, but the SO_2 for PT kids was significantly lower throughout the study period (*P* = .05).
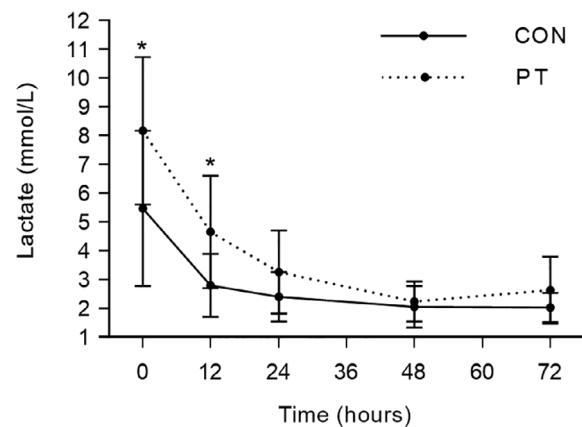

FIGURE 1 Mean blood L-lactate (mmol/L) concentrations over time for PT (dotted line) and CON (solid line) groups. Each error bar represents 1 SD from the mean. Asterisks (*) denote a significant difference between groups at that time point (*P* < .05). CON, control; PT, pregnancy toxemia
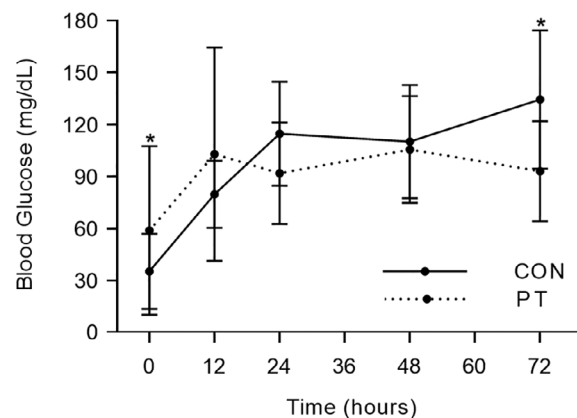

FIGURE 2 Mean blood glucose (mg/dL) concentrations over time for PT (dotted line) and CON (solid line) groups. Each error bar represents 1 SD from the mean. Asterisks (*) denote a significant difference between groups at that time point (*P* < .05). CON, control; PT, pregnancy toxemia
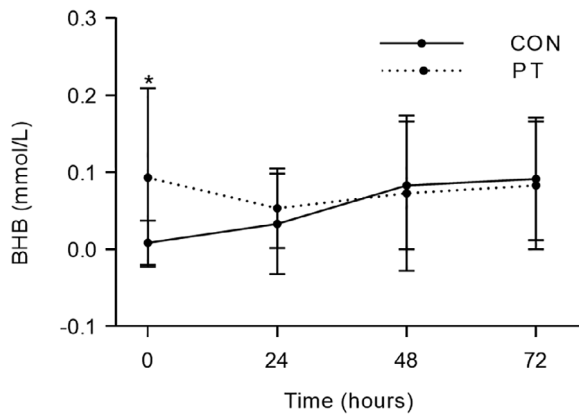
FIGURE 3   Mean BHB (mmol/L) concentrations over time for PT (dotted line) and CON (solid line) groups. Each error bar represents 1 SD from the mean. Asterisks (*) denote a significant difference between groups at that time point ($P < .05$). BHB, beta-hydroxybutyrate concentration; CON, control; PT, pregnancy toxemia

FIGURE 4   Arterial blood pH values for PT (diagonal lines) and CON (solid white) groups and times 0 and 72 hours. Asterisks (*) denote a significant difference between groups at that time point ($P < .05$). CON, control; PT, pregnancy toxemia

Mean blood pH for PT and CON kids was significantly different at both 0 and 72 hours. The PT group initially was significantly more acidemic than the CON group immediately after birth, but by 72 hours of age was significantly more alkalemic than the CON kids (Figure 4).

Base excess (BE), bicarbonate (HCO_3), and total carbon dioxide (TCO_2) all were significantly decreased in PT vs CON kids at time 0. After 72 hours of age, these variables were significantly increased in the PT as compared with the CON group. Arterial blood gas values are presented in Table 2.

3.7 | Packed cell volume and total protein concentration

Packed cell volume was significantly lower for PT vs CON kids at all time points (Figure 5). Total protein concentration also was significantly lower for PT vs CON kids at 24 and 72 hours ($P = .001$ and .02, respectively; Figure 6).

3.8 | Weight and average daily gain

No significant difference in weights at birth or 24 and 48 hours of age was identified. At 72 hours of age, CON kids had significantly higher mean weight compared to PT kids ($3.95 ± 0.93$ kg vs $2.98 ± 0.93$ kg, $P = .05$). In addition, average daily gain over the first 72 hours was significantly higher in CON kids compared to PT kids, with PT kids having a net loss of weight over the first 72 hours ($0.082 ± 0.17$ kg and $−0.12 ± 0.23$ kg, respectively, $P = .02$; Figure 7).

3.9 | Short-term morbidity and mortality

The CON kids were 1.3 times more likely to survive to discharge than were PT kids (95% CI = 1.01-1.77). Significantly more PT kids
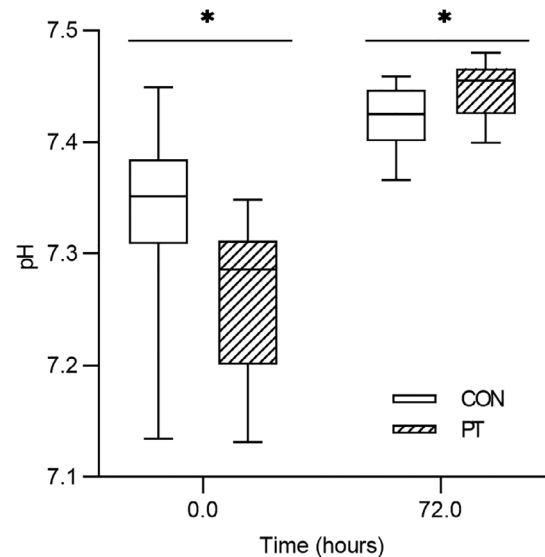
displayed abnormal nursing behavior and weakness shortly after birth compared to CON kids ($P = .04$). The PT kids were 1.45 (95% CI = 1.05-2.02) times more likely to not nurse soon after birth and 1.72 (95% CI = 1.04-2.84) times more likely to exhibit abnormal nursing behavior by 12 hours. More PT kids required tube feedings at 0 and 12 hours of age ($P = .005$ and .001, respectively) and more CON kids were successfully nursing the dam on their own at 0 and 12 hours of age ($P = .01$ and .001). The PT kids were 7.7 (95% CI = 1.13-52.45) times more likely to require tube feeding at birth and 2.8 (95% CI = 1.39-5.65) times more likely to require tube feeding at 12 hours of age. The 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. No significant difference was found in kids requiring bottle-feeding at either 0 or 12 hours of age.

The source of colostrum was significantly different between the PT and CON groups ($P = .005$). All of the CON kids received colostrum sourced solely from the dam. Of the PT kids, 4/16 received colostrum replacer only, and 3/16 received a mixture of the dam's colostrum and replacer. 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 concentration < 5.4 g/dL[11]) than kids that received either mixed or dam's colostrum alone.

The following variables were significantly higher in PT survivors compared to PT nonsurvivors: weight at birth ($3.26 ± 0.41$ vs $2.46 ± 0.17$ kg, $P < .001$), blood pH at birth ($7.28 ± 0.064$ vs $7.18 ± 0.013$, $P = .03$), PCV at birth ($37\% ± 0.58$ vs $30\% ± 1.33$, $P = .001$), blood L-lactate concentration at 12 hours ($5.2 ± 1.64$ vs $1.9 ± 0.05$ mmol/L, $P = .001$), and blood glucose concentration at 12 hours ($117 ± 57.53$ vs $32 ± 12.73$ mg/dL, $P = .001$). When nursing

TABLE 2 Arterial blood gas values for PT and CON groups at time 0 and 72 hours of age

	Time = 0 hour			Time = 72 hours		
	PT	**CON**	**P value**	**PT**	**CON**	**P value**
pH	7.26 ± 0.069	7.34 ± 0.079	.003*	7.45 ± 0.027	7.42 ± 0.028	.05*
Base excess	−5.8 ± 3.56	−1.8 ± 3.72	.01*	3 ± 3.67	−1.7 ± 3.58	.003*
HCO_3^- (mmol/L)	22 ± 2.79	24 ± 2.82	.02*	27 ± 3.37	23 ± 3.58	.005*
TCO_2 (mmol/L)	23 ± 2.84	25 ± 2.77	.02*	28 ± 3.4	24 ± 3.7	.006*

Note: All values are presented as mean ± SD. Asterisks (*) denote a significant difference ($P < .05$) between the two groups at that time point.
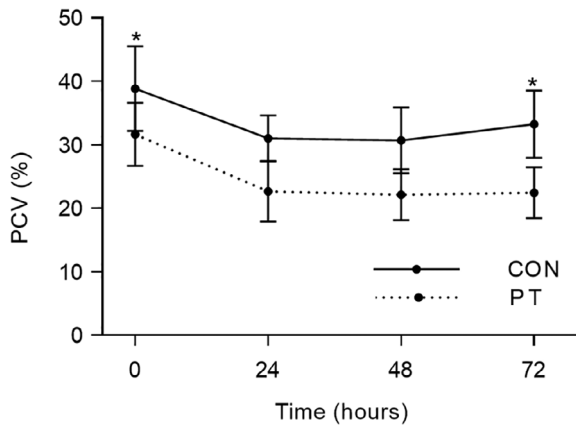Abbreviations: CON, control; PT, pregnancy toxemia.

FIGURE 5 Mean PCV results over time for PT (dotted line) and CON (solid line) groups. Each error bar represents 1 SD from the mean. Asterisks (*) denote a significant difference between groups at that time point ($P < .05$). CON, control; PCV, packed cell volume; PT, pregnancy toxemia
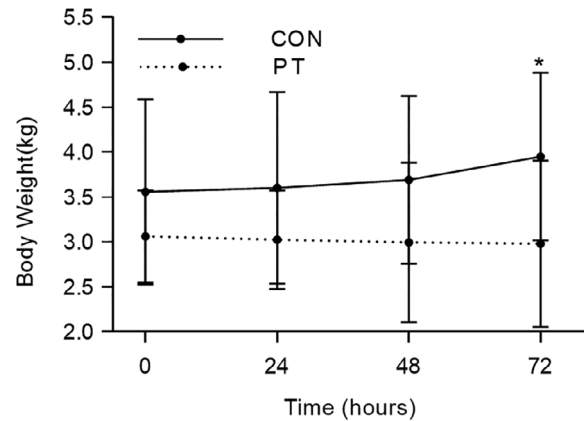

FIGURE 7 Mean body weight (kg) over time for PT (dotted line) and CON (solid line) groups. Each error bar represents 1 SD from the mean. Asterisks (*) denote a significant difference between groups at that time point ($P < .05$). CON, control; PT, pregnancy toxemia

FIGURE 6 Mean TP concentrations over time for PT (dotted line) and CON (solid line) groups. Each error bar represents 1 SD from the mean. Asterisks (*) denote a significant difference between groups at that time point ($P < .05$). CON, control; PT, pregnancy toxemia; TP, total protein
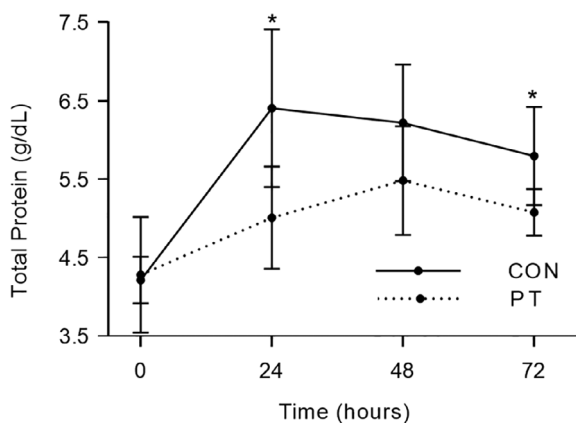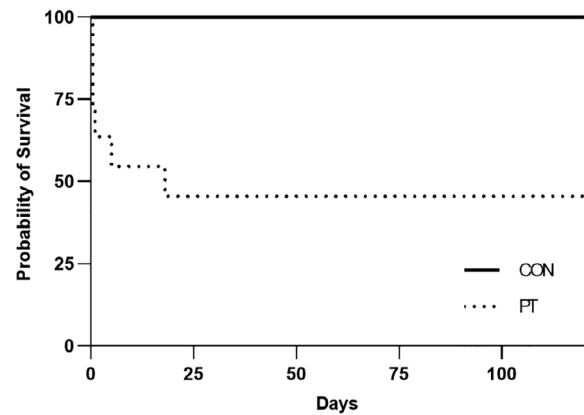

FIGURE 8 Kaplan-Meier survival curve for PT kids (dotted line) and CON kids (solid line) with data censored at 120 days. CON, control; PT, pregnancy toxemia

behavior of survivors and nonsurvivors was compared within the PT group, significantly more nonsurvivors had abnormal nursing behavior and weakness at 0 and 12 hours ($P = .01$ and .03, respectively).

3.10 | Long-term morbidity and mortality

Long-term follow-up was available for 12/12 CON kids and 11/16 PT kids. A significant difference in long-term survival was found between CON and PT groups at 3 months ($P = .02$). CON kids were 2.2

(95% CI = 1.152-4.20) times more likely to survive to 3 months than PT kids (Figure 8).

4 | DISCUSSION

Our findings showed an effect of PT on short- and long-term morbidity and mortality in goat kids. Pregnancy toxemia also had significant effects on blood L-lactate and blood glucose concentrations, and acid-base balance of kids in the first 72 hours of life.

We found an increase in the incidence of dystocia for PT does, but this increase was not statistically significant.. This finding is in contrast to a previous finding of increased incidence of dystocia in ewes with PT.[8] This disparity could indicate that our study lacked power to find a statistical difference, and dystocia cannot be dismissed as a potential confounding factor. Calves that experience dystocia have been shown to be at higher risk of weakness, prolonged recumbency, and decreased suckle response compared to calves from normal births.[13] Another study found that perinatal mortality (<12 hours) and general neonatal mortality (12 hours to 45 days) were higher in calves that experienced dystocia.[14] These calves also were shown to be at increased risk of neonatal disease in the first 45 days of life.[14]

Pregnancy toxemia kids were significantly more acidemic than CON kids. All kids in our study were sampled within 1 hour of birth after they were stable and breathing autonomously. They were maintained in sternal recumbency during sampling because it has been shown that lateral recumbency can decrease PaO_2 by as much as 30 mm Hg[15]. All kids were placed on nasal oxygen immediately postpartum, which was removed for at least 5 minutes before sampling so as not to affect PaO_2 results.[16] Another study compared umbilical cord blood between fetuses from PT and control does, and found that PT fetuses were significantly more acidemic in utero compared to controls.[17] The acidemia seen in the PT kids of our study was not as severe as seen in the cord blood analysis of PT fetuses in the other study (7.26 ± 0.069 vs 6.94 ± 0.29). The higher pH observed in our study could reflect the onset of alveolar ventilation and the less hypoxic extra-uterine environment. Additionally, it could be attributed to a difference in sample types because the cord blood samples in the previous study were oxygen-poor (venous-like)[17] and our study evaluated arterial samples. However, the pH of the control groups in our study and the previous study[17] do not show the same disparity (7.34 ± 0.079 vs 7.35 ± 0.12), which makes it unlikely that sample type alone explained the differences. Another possibility is that the does in the previous study[17] were more severely affected by PT than the does in our study, with likely more substantial compromise of placental gas exchange and nutrient transport. The differences seen in BE, HCO_3, and TCO_2 in the previous study[17] all were consistent with the differences seen between CON and PT kids in our study. However, we did not identify a significant difference between PT and CON for $PaCO_2$ and PaO_2, as was seen in the previous study.[17] Blood L-lactate concentrations were significantly higher in PT kids in our study and in the previous in utero study.[17] This strong anion likely contributes to the metabolic acidosis of PT kids.

Blood L-lactate concentrations reflect poor tissue perfusion and tissue oxygenation. In foals, venous lactate concentration is normally higher than the adult reference range at birth, but decreases over the first 24 to 48 hours.[18] In our study, both groups showed similar changes in L-lactate concentration over the first 48 hours, but PT kids had significantly higher blood L-lactate concentrations until 24 hours of age. This finding could reflect poor oxygenation because of hypoventilation in PT kids vs CON kids or a decrease in lactate clearance by the kidney and liver. The PT kids were more likely to be premature, which in foals was suggested to result in higher L-lactate concentrations.[19] In sick foals, a decrease in lactate at 24 hours after hospitalization correlated with increased survival.[18] Interestingly, in our study, PT kids that subsequently died had lower blood L-lactate concentrations at 12 hours of age when compared with survivors. This finding could reflect depletion of glycogen and adipose tissue stores and increased use of lactate as an energy substrate in the nonsurviving kids.

Blood glucose concentrations were significantly lower in CON kids compared to PT kids at birth. The relative hyperglycemia in PT kids could represent transient insulin resistance resulting from maternal glucose-insulin imbalance as seen in lambs born to undernourished ewes in late gestation[5] and with human infants born to women with gestational diabetes.[20] Another reason for hyperglycemia in PT kids could be exposure to exogenous glucocorticoids as part of the induction of parturition. However, studies in sheep and rats show that maternal treatment with glucocorticoids does not increase neonatal presuckling blood glucose concentration.[21,22] Foals and calves normally have blood glucose concentrations immediately postpartum lower than the juvenile reference range. The PT kids apparently were not able to increase their blood glucose concentration to that of CON kids in the subsequent 72 hours. Except for time 0 samples, which all were presuckle, there was no standardization of when feeding occurred before sampling for blood glucose concentrations in our study. This could explain the large variation in blood glucose concentrations obtained among the kids in the PT group.

The increase in blood BHB concentrations in PT kids immediately postpartum could reflect an increase in the rate of lipolysis, but no significant difference in NEFAs was found between the 2 groups in our study. In a study of maternal feed restriction in late gestation does, male kids born to undernourished dams had decreased NEFA concentrations compared to controls, suggesting they mobilized their body reserves less at birth.[23] The increase in BHB at birth simply may reflect transplacental acquisition of maternal BHB.

The respiratory system of PT kids at 72 hours was not as well adapted to extra-uterine life as it was in CON kids. The SO_2 was significantly lower in PT kids compared with CON kids, suggesting a relative hypoxemia and likely hypoventilation. The only arterial blood gas results outside of reference intervals for the PT kids at 72 hours were SO_2 and PaO_2. The SO_2 is a measure of the oxygen saturation of hemoglobin and PaO_2 reflects how efficiently oxygen is exchanged from the lungs to the blood. The differences seen with the PT kids at 72 hours were predictable using the oxygen-hemoglobin dissociation curve, where a PaO_2 of 60 mm Hg and SO_2 of 90% represent the

shoulder of the curve. This suggests that the decrease in both results is a consequence of inefficient transfer of oxygen from the alveoli to the blood because of immaturity of the lung, surfactant deficiency, acute lung injury (respiratory distress syndrome), atelectasis, or altered pulmonary vascular reactivity. A similar pattern of hypoxemia can occur with continued right-to-left shunting of blood, but cyanosis and marked dyspnea should be observed in such patients. The relative increases in arterial pH, BE, HCO_3, and TCO_2 in PT compared to CON kids at 72 hours indicate metabolic compensation for the relative hypercapnia of PT kids.

Kids in both groups had decreased PCV throughout the study period. We originally suspected this decrease could be a result of blood loss for sampling purposes, but further investigation determined that possibility to be unlikely. The cumulative sample volume was approximately 13 mL from each kid. This amount represents <1% blood volume by average weight in each group. This amount of blood loss is unlikely to have an appreciable effect on PCV. The PT kids were more anemic than the CON kids. Pregnancy toxemia might play a role in decreased production of fetal red blood cells. Decreased PCV in PT kids at birth was associated with increased risk of nonsurvival.

Plasma TP concentration was significantly lower in PT kids than in CON kids after 24 hours. A TP concentration of 5.4 g/dL in goat kids correlated to a serum immunoglobulin concentration of 12 g/dL, indicative of adequate passive transfer at 48 hours of age.[11] Although CON kids had significantly higher PCV, no difference was found in the frequency of failure of passive transfer (FPT) between groups. Studies of passive transfer in calves found that, regardless of the cutoff for adequate passive transfer, a higher TP concentration correlates with more positive health and performance outcomes later in life.[24-26] In our study, kids were either tube fed or bottle fed 10% of their body weight with the dam's colostrum or colostrum replacer to avoid FPT. This intervention likely lowered the rate of FPT in PT kids. The PT kids were more likely to need colostrum replacer because of inadequate colostrum production by the dam. Pregnancy toxemia can cause a decrease in colostrum production.[8,27] Parity also affects the quality and quantity of colostrum made by the dam, but in our study all does were multiparous.[28,29] No significant difference was found in FPT for PT kids that received both colostrum replacer and the dam's colostrum. Kids that received colostrum replacer alone were more likely to experience FPT. This difference could be caused by poor efficacy of the colostrum replacer, delayed abomasal emptying time, or poor absorption in the FPT kids. It is likely that kids that nursed the dam were receiving >10% of their body weight, which could have contributed to their decreased rate of FPT. Additionally, PT kids more frequently required tube feeding. Hypoxia, acidosis, and tube feeding can have variable but sometimes negative effects on efficiency of absorption of immunoglobulins in calves.[30-32]

In our study, no significant difference was found between weights of PT and CON kids until 72 hours. The PT kids were much more likely to lose weight over the first 72 hours of life, which was associated with nonsurvival at 3 months of age. In another study, kids born to undernourished dams had smaller abdominal girth, body mass index, and density index at birth when compared to control kids, and male kids born to undernourished dams had lower birth weight than

male control kids. However, no significant differences were found between restricted diet and control group kids thereafter in either weight or morphometric measurements taken at weekly intervals until slaughter at 6 weeks of age.[23]

Short- and long-term morbidity and mortality were significantly higher for PT kids compared to CON kids in our study. Short-term nonsurvival among PT kids was associated with lower birth weight, more severe acidemia at birth, lower PCV, and lower blood L-lactate and blood glucose concentrations at 12 hours of age. Premature kids were not at an increased risk for short-term mortality but were at increased risk for nonsurvival to 3 months. Although substantial loss of follow-up occurred for PT kids (5/16), dystocia and net weight loss in the first 72 hours were risk factors for nonsurvival to 3 months. Loss of long-term follow-up is an important limitation of our study, and these results should be interpreted with caution.

In summary, PT is associated with several risk factors for unthrifty kids, including an increase in dystocia, abnormal nursing behavior, weakness, and a decrease in cardiopulmonary efficiency. The effect of PT on neonatal insulin-glucose regulation warrants further investigation. Our sample size was rather small. There was variation in the severity of disease in the PT does and no control for different treatments and their potential effects on these results. Despite these limitations, we observed a difference in PT kids compared to CON kids in peripartum respiratory function, energy reserves, and energy mobilization. Most abnormalities in blood L-lactate and blood glucose concentrations, and arterial blood gas results were resolved by 48 to 72 hours, but ventilation in PT kids remained impaired 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 using bottle or tube feedings. Future research studies should control for the incidence of dystocia.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

All protocols and procedures described in this study were approved by the IACUC of Oklahoma State University.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

Leslie F. Weaver 🆔 https://orcid.org/0000-0001-5071-8377
Melanie J. Boileau 🆔 https://orcid.org/0000-0001-7350-7847

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