Definition of prepartum hyperketonemia in dairy goats

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ABSTRACT

A prospective cohort study was conducted on 1,081 dairy goats from 10 commercial herds in Québec (Canada) to define prepartum hyperketonemia based on optimal blood β -hydroxybutyrate acid threshold values for the early prediction of pregnancy toxemia (PT) and mortality in late-gestation dairy goats. All pregnant goats had blood sampled weekly during the last 5 wk of pregnancy. The blood was analyzed directly on the farm for β -hydroxybutyrate acid quantification using a Precision Xtra meter (Abbott Diabetes Care, Saint-Laurent, QC, Canada). Body condition scores on the lumbar region and sternum were noted. Each goat was classified as being at low ($n = 973$) or high risk ($n = 108$) of having PT by producers based on a standardized definition. The optimal threshold for predicting a PT diagnosis or mortality for each week before kidding was determined based on the highest sum of sensitivity and specificity. The association between hyperketonemia and subsequent PT was tested using a multivariable logistic regression model considering hyperketonemia at wk 4 prepartum, litter size, and body condition score at wk 4 prepartum as covariates, and herd and parturition cohort as random effects. The association between mortality and hyperketonemia was also tested using a logistic regression model accounting for the presence or absence of treatment during the last month of pregnancy. The hyperketonemia definition based on PT varied between ≥ 0.4 and ≥ 0.9 mmol/L during the last 5 wk prepartum. Goats affected by hyperketonemia at wk 4 prepartum and with a large litter size (≥ 3 fetuses) had 2.1 and 40.5 times the odds, respectively, of subsequent PT than other goats. Hyperketonemia definitions based on mortality varied between ≥ 0.6 and ≥ 1.4 mmol/L during the last 4 wk prepartum, and was ≥ 1.7 mmol/L during the first week postpartum. Goats affected by hyperketonemia and treated by producers had 3.4 and 11.8 times the odds, respectively, of subsequent mortality than did other goats. These results showed that

prepartum hyperketonemia could be defined in dairy goats using subsequent risks of PT or mortality during the last month of pregnancy.

Key words: dairy goat, β -hydroxybutyric acid, hyperketonemia, pregnancy toxemia

INTRODUCTION

Hyperketonemia is defined as an elevated concentration of ketone bodies in blood, serum, or plasma (Duffield et al., 2009). In ruminants, concentration of BHBA is commonly used to quantify energy balance during the last weeks of pregnancy and during the first weeks of lactation (Herd, 2000). In dairy goats, the last month of pregnancy is a critical period for the management of energy balance because 60 to 80% of the fetus' growth occurs during this period (Twardock et al., 1973; Rook, 2000) and because DMI is reduced simultaneously (Morand-Fehr, 1989). Therefore, a state of negative energy balance can occur during this period (Herd, 2000). An excessive negative energy balance prepartum can be identified by the presence of hyperketonemia (Sadjadian et al., 2013).

Prepartum hyperketonemia can be clinical (pregnancy toxemia; **PT**) or subclinical (Herd, 2000; Radostits et al., 2007; Brozos et al., 2011), although specific data in goats are not well described. Pregnancy toxemia, which is commonly seen during the last month of pregnancy in goats or sheep, generally has a low morbidity rate (2–5%) but a high mortality rate (80%; Brounts et al., 2004; Zamir et al., 2009; Brozos et al., 2011). Risk factors for PT include carriage of multiple fetuses, greater age, and extreme (fat or thin) BCS (Rook, 2000; Brozos et al., 2011). Clinical signs of PT are usually nonspecific at the beginning of the disease and may include anorexia, isolation from herdmates, distal limb edema, depression, prolonged recumbency, and weakness. If disease lasts more than 3 to 6 d, the symptoms generally progress to lateral recumbency, blindness, nystagmus, star-gazing, tremors, ataxia, coma, and death (Andrew, 1997; Rook, 2000; Brozos et al., 2011).

Early identification of goats at risk of developing PT could increase the chances of recovery (Rook, 2000; Brozos et al., 2011). The use of BHBA concentrations

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in blood was shown to be an interesting parameter for diagnosing PT (Henze et al., 1998), and prepartum hyperketonemia could be used to identify, earlier, animals at high risk of subsequent PT. Unfortunately, no prepartum BHBA threshold values have been validated to define hyperketonemia to predict PT. A blood threshold of ≥ 0.8 mmol/L was proposed for dairy sheep as an acceptable value (Panousis et al., 2012). Many veterinarians currently use this value in dairy goats because of the absence of specific goat information (Bani Ismail et al., 2008; Sadjadian et al., 2013). However, it remains unknown whether or not this value is relevant in dairy goats of North America.

Recently, the use of a handheld device for on-farm blood BHBA quantification in dairy goats has been validated (Doré et al., 2013; Pichler et al., 2014). In the aforementioned studies, the Precision Xtra (Abbott Diabetes Care, Saint-Laurent, QC, Canada) handheld meter showed a near-perfect correlation between its results and those of the gold standard test, the colorimetric enzymatic reaction with an automated serum analyzer (Doré et al., 2013). Therefore, this device could be used for blood BHBA quantification for on-farm surveillance of hyperketonemia.

The main objective of the present study was to define prepartum hyperketonemia in dairy goats based on finding the optimal BHBA thresholds for predicting subsequent risk of developing PT using the Precision Xtra handheld meter. Another objective was to define prepartum hyperketonemia based on finding the optimal threshold for predicting subsequent risk of mortality.

MATERIALS AND METHODS

A prospective cohort study was conducted from January 2012 to December 2013. Herd selection was based on convenience, with herds located within a radius of 200 km from the bovine ambulatory clinic of the Université de Montréal (Saint-Hyacinthe, QC, Canada), herds having regular DHIA testing (every month), and herds having a history of multiple PT cases over the last 2 yr. Sample size calculation was based on finding a significant difference between prevalence of PT in groups with normal and abnormal ketonemia values in blood. An a priori estimated difference of 14% in the prevalence of PT between goats with normal ketonemia (PT: 1%) and hyperketonemic goats (PT: 15%) when considering α and β errors of 5 and 20%, respectively, and an estimated prevalence of hyperketonemia of 5% in the study population were used for sample size calculation. The Animal Care Committee of the Université de Montréal approved this project.

Farm Sampling

A veterinarian and a research technician visited the participating herds weekly, starting 5 wk before the anticipated kidding date until at least 95% of the group had kidded. At each farm visit, a blood sample was collected from the jugular vein from each goat and blood BHBA was quantified while on the farm (Precision Xtra, Abbott Diabetes Care). The analytical sensitivity of the BHBA assay was 0.1 mmol/L. The inter- and intraassay coefficients of variation were 5.3 and 3.7%, respectively (Doré et al., 2013). The blood results were blinded to the producers. A lumbar and sternal BCS estimation using a 0.5-point scale (0 to 5; Hervieu and Morand-Fehr, 1999; Morand-Fehr and Hervieu, 1999) was performed at each farm visit by the same person.

Data Recording

For each goat, producers had to record information on kidding period (number of newborn kids, kids alive after 48 h, presence or absence of dystocia) and health during the last month of pregnancy and the first week of lactation. Targeted information included goat identity, breed, farm name, litter size, number of stillbirths (fetus died in uterus), number of goats kids still alive 48 h after birth, and all treatments given before kidding.

Definition of the Outcomes of Interest

Because no gold standard exists for defining PT, producers were provided a standardized chart summarizing the clinical signs of PT: prolonged recumbency, weakness, partial to complete anorexia, teeth grinding, depression, ataxia, limb swelling, lateral recumbency, blindness, tremors, convulsion, coma, and death (Rook, 2000; Brozos et al., 2011). Definition of PT was based on the presence or absence of those different clinical signs. To reduce variation on definition of PT from farm to farm, only one person presented this chart to the producers and the definition of PT was repeated to each producer at the beginning of every month of data collection to standardize the outcome definition. At the end of the data collection or at time of death for the goat, the producers scored each goat for presence of PT, based on a 4-point scale (absence, low, moderate, or strong suspicion of PT) using the previously defined chart.

The second outcome of interest studied was mortality during the last month of pregnancy and the first week of lactation. Goats that died were classified as dead before parturition or during the first week following parturition, depending on the time of death.

Statistical Analyses

Determination of BHBA Threshold to Predict PT. To determine if goats at high risk of PT and goats at low risk of PT had different prepartum BHBA values, we used a mixed linear regression model (PROC MIXED, SAS 9.3, SAS Institute Inc., Cary, NC) using repeated measures and accounting for the clustering effect of goats within herds and parturition cohorts. Based on this approach, the 4 initial PT strata were collapsed into a dichotomous PT variable: 1 = low risk of PT (pooling goats with absence and low suspicion of PT) and 2 = high risk of PT (pooling goats with moderate and strong suspicion of PT). A comparison of mean values of BHBA at each week between both groups was assessed using least squares means and a Tukey-Kramer test after transforming the BHBA values into logarithmic values.

Data from the last 5 wk of pregnancy were used to determine BHBA thresholds. For this purpose, the BHBA data of wk 5 prepartum were dichotomized using multiple cut-off values (from ≥ 0.2 to ≥ 2.5 mmol/L in increments of 0.1 mmol/L). The risk of developing PT was then compared between animals with and without hyperketonemia using all previously mentioned BHBA thresholds (PROC FREQ in SAS). For each 2×2 contingency table, the sensitivity (Se) and specificity (Sp) of the threshold for predicting subsequent PT were calculated, as well as the Pearson Chi-squared test result. Sensitivity was defined as the number of hyperketonemic goats divided by the total number of PT goats, whereas Sp was defined as the number of nonhyperketonemic goats divided by the number of non-PT goats. The blood BHBA threshold that had the greatest sum of sensitivity and specificity was selected as the optimal threshold for that week. The same approach was used for defining hyperketonemia in wk 4, 3, 2, and 1 prepartum. In the end, one threshold value was retained by week and used for further modeling. Spearman rank-order correlation coefficients (PROC CORR in SAS) were calculated between all weeks. Variables associated with a high correlation ($\rho > 0.5$) were not included in the same multivariable model.

Multivariable mixed logistic regression models accounting for herd and parturition cohort clustering effects and considering PT as a dependent variable were used (PROC GLIMMIX, in SAS). The multivariable models were built using a backward elimination strategy. Hyperketonemia (**Hyper**) at wk 5 prepartum to wk zero (Hyper-5, Hyper-4, Hyper-3, Hyper-2, Hyper-1, and Hyper0) were included in the models. To represent field conditions, hyperketonemia at wk 4 prepartum (Hyper-4) was forced on all models because this period is routinely used for body condition scoring

and feeding adjustment (Morand-Fehr, 2005). A first model was computed considering all available variables. A second model was computed considering all variables when forcing Hyper-4 and litter size to represent field conditions, where litter size is frequently unknown until parturition. All biologically relevant 2-way interactions between Hyper-4 and other covariates were tested in models and retained if significant at $P < 0.05$.

A third multivariable model was constructed to evaluate if more than one positive test may influence the risk of PT. To create this model, a new variable (toxfreq) was created using the number of times blood BHBA values were found at or above the different cut-offs for each 5 wk before kidding. A value of 0, 1, 2, or 3 was assigned to each goat, depending of the number of times they presented a blood BHBA value at or above the cut-offs defined previously (0, 1, 2, and ≥ 3 positive tests, respectively). The toxfreq variable was then included as a categorical variable in a mixed logistic regression model, accounting for herd and parturition cohort clustering effects and considering PT to be a dependent variable (PROC GLIMMIX in SAS).

Determination of BHBA Threshold to Predict Mortality. To determine if goats at low and high risk of mortality had different prepartum BHBA values, we used a mixed linear regression model (PROC MIXED, SAS 9.3, SAS Institute Inc.), using repeated measures and accounting for the clustering effect of goats within herds and parturition cohorts. All initial mortality strata were collapsed into a dichotomous mortality variable: 1 = alive (pooling goats that were still alive 1 wk after parturition) and 2 = dead (pooling goats that died during the last month of pregnancy and the first week after parturition). A comparison of mean values of BHBA for each week between both groups was assessed using least squares means and the Tukey-Kramer test.

To determine the optimal BHBA thresholds for identifying goats at high risk of mortality during the last month of pregnancy and the first week of lactation, we used the approach presented in the previous section for predicting PT. The BHBA values for each week (wk 5 before kidding to wk 0) were transformed into a dichotomous variable. The blood BHBA threshold value for each week having the greatest sum of Se and Sp was selected as the optimal threshold. The definitions of Se and Sp were similar to those previously described but considering mortality as a true state of disease instead of PT. In the end, one threshold value was retained by week and used for further modeling. Spearman rank-order correlation coefficients (PROC CORR in SAS) were calculated between all weeks. Variables associated with a high correlation ($\rho > 0.5$) were not included in the same multivariable model.

A multivariable mixed logistic regression model (PROC GLIMMIX in SAS), accounting for herd and parturition cohort clustering effects and considering mortality as a dependent variable, was built. The variables Hyper-4 and presence or absence of treatment were forced on the model. Presence or absence of treatment was included in the model because we considered it an important risk factor for mortality. A backward elimination process considering all available variables was used to build the model. All biologically relevant 2-way interaction terms were offered to the model.

RESULTS

Descriptive Statistics

A total of 1,242 dairy goats from 10 commercial dairy farms were enrolled. Of the total number of goats enrolled in the project ($n = 1,242$), 161 goats were excluded for not being pregnant ($n = 116$) or for kidding after the sampling period ($n = 45$). Overall, data from 1,081 dairy goats were used in this study. The study was conducted over 4 parturition cohorts corresponding to 2 kidding periods in spring (February to May 2012 and 2013) and 2 kidding periods in the end of summer or fall (August to November 2012 and 2013). In this study, mean herd size was 407 (ranging from 175 to 1,000) with a herd average 305-d mature-equivalent milk production of 870 kg (ranging from 640 to 1,050 kg). A proportion of 3% of the enrolled goats were in first lactation, 36% in second lactation, 56% in third or greater lactation, and 5% unknown. Breed distribution in the study was 45.6% Alpine ($n = 493$), 43.7% Saanen ($n = 472$), 10.0% LaMancha ($n = 109$), 0.4% Nubian ($n = 4$), and 0.3% cross-breed ($n = 3$).

Pregnancy Toxemia

Based on the standardized chart of the PT definition, 973 goats were classified as low risk for PT and 108 classified as high risk for PT in this study. The overall prevalence of animals at high risk for PT was 10% (herd-level prevalence varied from 0 to 18%) in this study. The comparison of means BHBA between groups at low risk and at high risk of PT shows a significant difference from wk -5 to wk 0 ($P < 0.05$; Figure 1).

The optimal BHBA thresholds based on the maximal sum of sensitivity and specificity to identify animals at high risk of having PT are summarized in Table 1. These values varied between ≥ 0.4 and ≥ 0.9 mmol/L over the last 5 wk prepartum.

Logistic regression models quantifying the risk of PT 4 wk before kidding are presented in Table 2. In all models, Hyper-4 prepartum was significantly associ-

ated ($P < 0.01$) with the odds of subsequent PT. Litter size was also associated ($P < 0.01$) with the odds of subsequent PT, but only when comparing 3 fetuses or more to a singleton. Although mean BCS 4 wk before kidding was associated with a greater risk of developing PT in fat goats (14.4%) compared with thin (7.7%) and normal goats (7.8%) in univariable models, it was not significant in multivariable models. In the logistic regression model considering the frequency of weekly hyperketonemia during the last 5 wk of pregnancy, this variable was significantly associated with PT when there were 2 (odds ratio = 5.2, 95% CI: 1.8 to 18.5; $P < 0.02$) or more positive tests (odds ratio = 18.1, 95% CI: 6.3 to 52.5; $P < 0.01$; Table 2).

Mortality

During this study, the overall mortality rate was 5.5% from prepartum until 1 wk postpartum. The herd-level mortality rate varied from 0 to 11.7%, and the median value was 4.8%. The mortality proportion associated with PT during this period was 72% of all cases. The mortality rate was 38.9% in the group at high risk of PT and 1.6% in the group with a low risk of PT. The comparison of means BHBA between the groups at low and high risk of mortality shows a significant difference from wk -4 to wk 0 ($P < 0.05$; Figure 1).

The optimal BHBA thresholds based on the maximal sum of Se and Sp to predict mortality are described in Table 3. These values varied between ≥ 0.6 and ≥ 1.7 mmol/L during the period that includes the last 4 wk prepartum and the first week postpartum.

A logistic regression model quantifying the risk of mortality 4 wk before kidding is presented in Table 4. In this model, hyperketonemia at wk 4 prepartum and the presence or absence of treatment during the last month of pregnancy were significantly associated ($P < 0.01$) with the odds of subsequent mortality.

DISCUSSION

Pregnancy Toxemia

To our knowledge, the present study is the first to define prospective hyperketonemia during the last month of pregnancy in goats. Such an approach allows for determination of the optimal BHBA threshold on a weekly basis for predicting greater odds of subsequent negative outcomes. Previous studies in dairy goats used a static threshold value to define subclinical PT during the last month of pregnancy. For example, values such as >0.86 mmol/L (Bani Ismail et al., 2008), ≥ 1.1 mmol/L (Brozos et al., 2011), or between 0.8 and 1.6 mmol/L (Sadjadian et al., 2013) have been reported

Figure 1. (A) Mean values of blood BHBA stratified by week prepartum for goats at low risk of pregnancy toxemia (■) and at high risk of pregnancy toxemia (●); (B) mean values of blood BHBA stratified by week prepartum for goats at low risk of mortality (alive; ■) and at high risk of mortality (dead; ●) enrolled in an observational study investigating prepartum ketonemia in dairy goats. *Significant difference ($P < 0.05$) within a week. Error bars represent standard errors of means.

to define subclinical PT in goats. Trevisi et al. (2005) used a different scale using low (<0.6 mmol/L), mild (0.6 to 1.09 mmol/L), and high (≥ 1.09 mmol/L) concentrations of BHBA in blood. Unfortunately, such an approach was subjective because (1) it did not account for a weekly variation of BHBA values, and (2) it did not use another test (clinical diagnosis or ancillary tests analysis) to objectively define PT. In the current study,

the final diagnosis of PT did not depend on the blood BHBA values, but instead was based on the observations of clinical signs, which we standardized across farms using a clinical chart.

It is likely that biases influenced the number of PT cases found in this study. For example, using clinical signs even with a standardized method across farm is predisposed to variability in the interpretation from

Table 1. Optimal BHBA thresholds for each week prepartum based on the maximal sum of sensitivity and specificity to predicting goats at a high risk of subsequent pregnancy toxemia

Week prepartum	BHBA threshold ¹ (mmol/L)	Goats at or above threshold ² (%)	Sensitivity (%)	Specificity (%)	<i>P</i> -value
5	≥0.4	33.0	61.8	69.8	<0.01
4	≥0.4	44.4	70.4	58.4	<0.01
3	≥0.5	25.6	63.3	78.5	<0.01
2	≥0.6	25.9	73.7	79.0	<0.01
1	≥0.9	14.6	60.5	89.7	<0.01

¹Blood BHBA value having the greatest sum of sensitivity and specificity for predicting subsequent risk of pregnancy toxemia.

²Proportion of goats with a blood BHBA value equal or greater to the threshold value.

one producer to another, especially for mild to moderate cases of PT. A producer's ability to detect sick animals and the time devoted to detect clinical signs of PT every day, especially in the middle of the kidding period, might have differed between farms. Similarly, cases showing nonspecific clinical signs such as anorexia, teeth grinding, depression, and weakness could have been associated with other diseases. For those reasons, some producer may have missed some cases or misinterpreted clinical signs. Herds with a high prevalence of PT may also be predisposed to identify earlier PT cases as positive compared with herds with low prevalence. This could be caused by greater attention to PT diagnosis by producers when herds have a high PT prevalence. Another bias possibly influencing the prevalence of PT in this study was the PT score used (absence, low, moderate, or strong suspicion). This score might have been better using fewer categories (i.e., only PT-positive or PT-negative). Definition of mild, moderate, and severe cases of PT requires a standardized case definition to reduce variation between observers when

interpreting cases of PT to reduce bias. Future studies should consider these limitations.

The use of different thresholds during the last weeks of pregnancy required a precise identification of the breeding date for each goat. Having breeding date information of goats in a herd is key in using the hyperketonemia definition identified in this study. Considering that the threshold value varies from ≥0.4 to ≥0.9 mmol/L during the last 5 wk of pregnancy, it may require excellent follow-up by the producer during the breeding period. One of the advantages to having good breeding date records is to be able to prepare the goats more efficiently, especially with a good transition period before the start of lactation (Morand-Fehr, 1989).

In the present study, litter size was associated with PT after accounting for hyperketonemia at wk 4 prepartum. It is known that increasing the size of the litter increased BHBA in the plasma of ewes during late pregnancy (Harmeyer and Schlumbohm, 2006), which could lead to PT. In a study on ewes, Zamir et al. (2009) reported a prevalence of PT varying from 0 to 33%,

Table 2. Final logistic models for predicting pregnancy toxemia when considering herd clustering in a study investigating prepartum hyperketonemia in 1,081 dairy goats

Model	Variable	No. of goats	Coefficient	SE	Odds ratio	95% CI	<i>P</i> -value
1	Hyperketonemia wk 4 prepartum ¹						
	No	513	Referent				
	Yes	410	1.42	0.36	4.14	2.05 to 8.35	<0.01
2	Hyperketonemia wk 4 prepartum ¹						
	No	506	Referent				
	Yes	390	0.72	0.35	2.07	1.03 to 4.14	0.04
	Litter size						
	1	169	Referent				
	2	529	1.88	1.05	6.58	0.84 to 51.72	0.2
	≥3	198	3.70	1.05	40.47	5.20 to 315.30	<0.01
3	Frequency of BHBA-positive tests						
	0	451	Referent				
	1	245	1.09	0.61	2.97	0.91 to 9.76	0.3
	2	147	1.74	0.60	5.21	1.77 to 18.46	0.02
	≥3	238	2.90	0.54	18.11	6.25 to 52.48	<0.01

¹BHBA value ≥0.4 mmol/L.

Table 3. Optimal BHBA thresholds for each week prepartum based on the maximal sum of sensitivity and specificity to predict mortality in dairy goats

Week prepartum	BHBA threshold ¹ (mmol/L)	Goats at or above threshold ² (%)	Sensitivity (%)	Specificity (%)	<i>P</i> -value
4	≥0.6	14.9	44.7	86.7	<0.01
3	≥0.6	19.8	65.4	82.7	<0.01
2	≥0.6	26.1	70.8	76.1	<0.01
1	≥1.4	8.2	51.3	93.5	<0.01
0	≥1.7	5.6	28.6	95.0	<0.01

¹Blood BHBA value having the greatest sum of sensitivity and specificity for predicting subsequent risk of mortality.

²Proportion of goats with a blood BHBA value equal or greater to the threshold value.

with litters of 1 to 6 lambs, and Moallem et al. (2012) reported that a significant increase of BHBA in litters with more than 3 lambs was associated with a greater risk of developing PT. Interestingly, the association of litter size in the present study with PT was significant even after accounting for prepartum hyperketonemia. Those results indicate that knowing litter size can be useful in identifying goats with a greater risk of developing PT. Monitoring litter size using ultrasonography after the breeding period could be useful in identifying goats with 3 or more fetuses. As this technique increases time and cost during a preventive visit, an economics study must be done to determine the cost of determining fetal count by ultrasound, depending of the number of goats to check and the expected prevalence of PT in the herd.

In our study, evaluation of BHBA in blood has shown the possibility of detecting goats at high risk of PT several weeks before clinical signs appear. An individual evaluation of each goat 1 mo before kidding could help to identify goats at greater risk of PT, as described by Brozos et al. (2011). Using the BHBA value at wk -4 to identify animals with hyperketonemia may help to reduce the incidence of clinical forms of the disease by providing an opportunity to treat the animals before clinical signs appear. The main disadvantage of this technique is the high prevalence of hyperketonemia in our study associated with a threshold of ≥0.4 mmol/L. At wk 4 prepartum, 44% of the goats were classified

as hyperketonemic. This may be due to the low specificity of the test (58.4%), the fact that the difference between the mean BHBA values from each group is relatively close 1 mo before kidding in our study, and the daily fluctuation of BHBA in goats, which is associated with other factors, such as time of feeding (Oetzel, 2004; Quiroz-Rocha et al., 2010; Mahrt et al., 2014) and other diseases (Brozos et al., 2011). An alternative method to increasing Se and Sp could be to test goats for hyperketonemia closer to the kidding period, but this approach would likely fail to detect early cases of PT when the chance of treatment success is considered higher. A better option could be to use weekly BHBA values in serial testing. As the frequency of positive tests during the last month was associated with the risk of developing PT in our study, using BHBA testing in a series (i.e., positive if 2 tests or more are higher to the cutoff) would lead to an increased specificity of the test and would decrease the false-positive fraction ($1 - Sp$).

Mortality

In this study, the mortality rate in the group at high risk of PT was 38.9%. This value is much lower than the 80 to 100% rate reported by other authors (Rook, 2000; Brounts et al., 2004; Zamir et al., 2009), but is still high from a herd management perspective. The reason for this lower mortality rate is unclear. This difference could be attributed to a greater number of

Table 4. Final logistic model for predicting mortality when accounting for herd clustering in a study investigating prepartum hyperketonemia in 1,081 dairy goats

Variable	No. of goats	Coefficient	SE	Odds ratio	95% CI	<i>P</i> -value
Hyperketonemia wk 4 prepartum ¹						
No	787	Referent				
Yes	138	1.22	0.47	3.37	1.34 to 8.52	0.01
Treatment						
No	808	Referent				
Yes	117	2.46	0.56	11.79	4.82 to 28.84	<0.01

¹BHBA value ≥0.6 mmol/L.

goats identified as having mild PT at an early stage while still showing only mild signs of the disease (such as partial anorexia, mild depression, and weakness), due to better observation of the goats by the owner during this study. The design of the study could also explain the lower mortality rate. Studies describing the PT mortality rate usually report terminal cases of the disease seen by veterinarians on the farm or at a hospital (Brounts et al., 2004; Tharwat et al., 2012). In our study, all stages of PT were seen due to the close follow-up of all goats during the study. We cannot exclude the possibility that some cases might have been falsely classified as sick despite the absence of PT because of the lack of gold standard for this disease.

The association between hyperketonemia at wk 4 prepartum and mortality was not surprising. Other authors reported an important increase of BHBA in terminal cases of PT (Zamir et al., 2009; Tharwat et al., 2012). Similarly, animals that received treatment during the study period were at greater risk of mortality. However, a weakness of our study was that treatments were not standardized on all farms. Some treatments might improve the condition of sick animals, but a randomized clinical trial would be necessary to answer this question. For example, in dairy cows, it has been shown that hyperketonemia is associated with detrimental outcomes (Duffield et al., 2009), but it has also been shown that administration of propylene glycol to early-identified hyperketonemic cows can improve their performance and survival (McArt et al., 2011, 2012). It is unclear at this point if it is the same in dairy goats.

It is well known and accepted that treatment of PT is based on administering energy sources and removing factors that increase energy requirements of affected animals (Rook, 2000; Brozos et al., 2011). The efficacy of treatment depends on early instigation, but usually treatment of clinical forms of PT is often associated with a low success rate (Rook, 2000; Brozos et al., 2011; Lima et al., 2012) and a high mortality rate (Brounts et al., 2004; Zamir et al., 2009; Lima et al., 2012). To our knowledge, there is a paucity of evidence concerning treatment efficacy in small ruminant PT. Treatment with oral administration of solution of glucose plus other electrolytes (Buswell et al., 1986) at 160 mL per os every 4 to 8 h until clinical signs ceased or the animal died have been somewhat successful in ewes, with 89.7% of full recovery ($n = 29$) for mild cases of PT and 55% of full recovery ($n = 49$) in severe cases of PT. Average number of doses given was 2.3 in ewes that survived and 4.1 in ewes that died. Another study, combining oral solution of glucose and injections of recombinant bST at 160 mg, showed a better recovery rate (58.8%, $n = 17$) in animals receiving both treatments compared with only oral drench (34.8%, $n = 23$;

Scott et al., 1998). Use of propylene glycol (60 mL per os once a day for 2 wk) combined with intravenous injection of 200 to 400 mL of dextrose 40% once a day for 5 to 9 d has shown an excellent success rate (100%, $n = 4$) in moderate to severe cases of PT (Andrew, 1982). Other treatments, such as use of flunixin meglumine combined with intravenous glucose (Zamir et al., 2009) and use of insulin (Henze et al., 1998) with oral solution of glucose, have also been reported. Finally, induction of parturition or cesarean section in the final stage of the disease was reported to have a poor prognosis for the fetus (mortality rate: 54%) and the doe (mortality rate: 89%; Lima et al., 2012). Variability in recovery rate from one study to another with the same treatment, variations in treatment protocols, and different definitions of PT from one study to another make it difficult to know which protocol is ideal for treatment of PT, especially in severe cases. More studies should be done to identify the best treatment option for PT. For this reason, the focus should be on preventing the disease and identifying animals at higher risk of developing PT.

CONCLUSIONS

Hyperketonemia in dairy goats can be defined by the optimal threshold values for predicting risk of developing PT and risk of mortality during the last month of pregnancy. Blood BHBA values in goats in wk 4 prepartum can be used to identify animals at greater risk of negative outcomes at an earlier stage of the disease. A therapeutic approach for these animals remains unclear and needs further investigation.

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