Effects of prophylactic propylene glycol administration at calving on subclinical ketosis in Holstein dairy cows

Research Article

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ABSTRACT

Forty-four Holstein dairy cows were randomly enrolled in the treatment group (group 1, n=19) or control group (group 2, n=25) at calving. Group 1 received prophylactic propylene glycol treatment (PPGT) (300 ml/cow, beginning at calving, total 3 days). The group 2 remained untreated. All animals were tested on blood and milk beta-hydroxybutyric acid (BHBA) at postpartum week 2 and 4 (PW2 and 4), body condition scores (BCS), average daily milk production (ADMP) and postpartum health disorders were monitored in 90 days in milk (90 DIM). The incidence of subclinical ketosis (SCK) was 8% and 4% in blood test (BHBA≥1.2 mmol/L) and by 12% and 24% in milk test (BHBA≥200 µmol/L) in group 2 at PW2 and PW4 respectively. SCK was not detected in group 1. The study cows lost BCS on postpartum days 30 and 60. ADMP was remarkably different between group 2 with SCK (28.36 kg), without SCK (34.36 kg) and group 1 without SCK (33.92 kg). Mastitis, metritis and laminitis incidence were observed both in group 1 and 2, but clinical ketosis and culling rate were observed in group 2 only. Mastitis incidence was 32% and 10.5% in group 2 and group 1 respectively. Culling rate was 12% in group 2, no culling was observed in group 1. Conclusively, although there wasn't a significant effect of PPGT on the averages of blood and milk BHBA at PW2 and 4, the observed incidence of SCK in group 2 in association with postpartum health disorders and ADMP loss may require selective PPGT in cows at risk of SCK, rather than treatment the entire whole population.

Keywords: Beta-hydroxybutyric acid, Holstein, milk yield, propylene glycol, subclinical ketosis

INTRODUCTION

Propylene glycol (PG) was frequently used in the pharmaceutical industry for different formulations (Jimenez et al., 2020; Mikuła et al., 2020), and it was also recommended for the prevention and treatment of hyperketonemia in dairy cattle (El-Kasrawy et al., 2020; Gordon et al., 2017; McArt et al., 2011; Zhang et al., 2020). Studies showed that oral PG application significantly changed the rumen fermentation pattern and decreased the molar ratio of acetate/propionate by increasing the predominant end-product propionate of PG fermentation in the rumen (Christensen et al., 1997; Nielsen, 2004). Hyperketonemia is a metabolic disease diagnosed by elevated ketone bodies in blood, milk and urine in dairy cattle (Deniz et al., 2020; Duffield et al., 2009). Subclinical ketosis (SCK) is defined by the increased ketone bodies in blood and milk without clinical signs, but it can cause production losses in dairy cow (Aksoy et al., 2022; Uyarlar et al., 2018). It is manifested by a high betahydroxybutyric acid (BHBA) concentration ≥1.2 mmol/L in the blood (Brunner et al., 2018; Gordon et al., 2017; Şentürk et al., 2016) and 100 µml/L (light) or ≥200 µml/L (severe) in the milk (Aksoy et al., 2022; Berge et al., 2014; McArt et al.,

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2012). SCK can cause milk production losses in average up to 300 kg per lactation (Deniz et al., 2020; Duffield et al., 2009), as well as increases the risk for metabolic and reproductive diseases and the culling rate (Aksoy et al., 2022; McArt et al., 2012; Uyarlar et al., 2018).

Worldwide prevalence of SCK was reported to be 22-24 % in blood (Brunner et al., 2018; Suthar et al., 2013; Şentürk et al., 2016) and 39% in milk tests (Berge et al., 2014). Oral propylene glycol drenching was frequently used in controlling SCK (Gordon et al., 2017; McArt et al., 2014). However, there were contradictory reports about the significant efficacy of prophylactic PG treatment (PPGT) in dairy cattle in the literature (Fonseca et al., 2004; Jeong et al., 2018; Lomander et al., 2012; Østergaard et al., 2020). Many well-cared-for and managed integrated dairy cattle farms use PPGT in the entire population at calving to reduce hyperketonemia and associated metabolic diseases in Turkey despite contradictory and doubtful reports are available about its significant effects.

The present study was conducted to investigate the effects of PPGT at calving on blood and milk BHBA concentrations, as well as on SCK incidence and associated milk production, body condition scores (BCS), culling rate, and metabolic diseases in a dairy Holstein farm.

MATERIALS AND METHODS

Study animals and groups

The present randomized and controlled study was conducted on an integrated dairy Holstein farm with an average of 315 lactating cows per period. Forty-four pregnant primiparous and multiparous dairy Holstein cows, which were close to calving were randomly enrolled in the study. Cows in the treatment group (group 1) (n=19) received 300 ml of oral PG drench (99.9%, Yongjam-ro, Nam-gu, Ulsan, Korea) on the day of calving, one day and two days after calving (total 3 consecutive days). Control group cows (group 2) (n=25) remained untreated. Subgroups for SCK positive or negative (with or without SCK) were created to evaluate the effects of hyperketonemia on milk production and postpartum metabolic problems (Aksoy et al., 2022; Brunner et al., 2018; Suthar et al., 2013).

Animal feeding

Ration content and calculated energy intake were presented in Table 1. Water was served ad libitum. The content of the ration was prepared by farm a veterinarian and consultant animal feeding expert. As a standard protocol of the farm for the controlling of milk fever, anionic feeding was initiated at the last 21 days of gestation and oral calcium boluses were administered at calving and 12 h later to all animals in the farm.

Blood collection, analysis and health checks

Blood was collected from the coccygeal vein to analyse BHBA by a cow-side BHBA-analyser (Khol et al., 2019) (Medtrust Wellionvet Belua, Med Trust Handelsges.m.b.H., Austria) at postpartum week 2 (PW2) and 4 (PW4). On the same days, milk BHBA was tested in 50 ml of freshly taken milk with milk-test-strips (Ketotest, Elanco Animal Health, Sanwa Kagaku Kenkyusho Co. Ltd., Nagoya, Japan). According to the manufacturer's instruction, this test strip showed different colours indicating 0, 50, 100, 200, 500, and 1000 µmol/L BHBA in the milk, which refer to the BHBA scores of 0, 0.5, 1.0, 2.0, 5.0, 10.0 respectively. SCK was defined by a cut-off point of BHBA≥1.2 mmol/L in the blood (Brunner et al., 2018; Gordon et al., 2017) and ≥200 µmol/L (BHBA score ≥2.0) in the milk (Aksoy et al., 2022; Benedet et al., 2019; Berge et al., 2014) as also recommended by the manufacturer of the test kits. BCS was evaluated according to Edmonson et al. (1989) on a scale from 1 to 5 at calving, 1 month and 2 months after calving.

Table 1. Content of the ration of the study cows as dry matter in close-up and early lactation.

Contents	Close-up	Early lactation
Maize silage (kg/day)	3.63	4.95
Hay (kg/day)	2.78	0.70
Alfalfa (kg/day) (17% protein)	2.08	4.06
*Concentrated milk feed (kg/day)	3.10	3.54
Maize flake (kg/day)	1.63	3.00
Cotton seed (kg/day)	0.00	1.35
Limestone (kg/day)	0.15	0.20
Soy sauce 46% protein (kg/day)	0.00	2.45
ByPass fat (kg/day)	0.00	0.50
**Vitamin, mineral and amino acid premix (kg/day)	0.12	0.12
Calcium chloride 77-80% (kg/day)	0.15	0.00
Ammonium sulphate (kg/day)	0.15	0.00
ME (Mcal/day)	32.1	54.3
NEI (Mcal/day)	20.1	34.9
DMI (kg/day)	13.7	20.8
Ca (%DM)	1.30	1.00
P (%DM)	0.30	0.40
DCAD (mEQ/kg)	-169	158

DM: dry matter, DMI: dry matter intake, ME: metabolizable energy, NEI: net energy intake, DCAD: dietary cation-anion difference. *Concentrated milk feed composed of 21 % crude protein, 4.2 % crude fat, 7.5 % crude cellulose, 23.4 % starch, 8.2 % crude ash. **Premix content: each 7,5 kg premix contains 1 mio IU of vitamin A, 350.000 IU of vitamin D3, 4.800 mg of vitamin E (50%), 100 mg of biotin (2%), 20 mg of vitamin B12 (1%), 4.000 mg of ferrous oxide (55%), 750 mg of organic ferrous (17%), 1.800 mg of copper oxide (21%), 6.000 mg manganese oxide 60%, 10.000 mg zinc oxide 75%, 1.000 mg of organic zinc (21%), 70 mg of sodium selenite (4.5%), 20 mg of organic selenium 0.3%, 100 mg of calcium iodate (62%), 40 mg of ethylene diamine dehydrate iodate (79.5%), 40 mg of cobalt sulphate 20%, 85.000 mg of choline chloride (25%), 30.000 mg of organic lysine (40%), 80.000 mg of organic methionine (55%), 2.000 g sodium bicarbonate (27% Na), 600.000 mg of magnesium oxide (82%), 87.500 mg of calcium (D.C.P 18% P and 15% Ca), 63.000 mg of phosphorous (D.C.P 18% P and 15% Ca), 200.000 mg sodium chloride (38% Na).

Average daily total milk production (ADMP) per cows was recorded with the automatic milking system (DeLeval 2 x 20 parallel speedy system) in 90 days in milk (90 DIM). All study cows in the groups were monitored and evaluated from the clinical health point of view, and any diseases or culling were registered immediately up to 90 DIM.

Statistical analysis

Statistical analyses were performed using the SPSS (SPSS 22, IBM SPSS Statistics®, Chicago, IL, USA) software and the results were evaluated for α=0.05. Mean (m) and standard error (se) were presented as descriptive statistics. Normality of the data were evaluated by Kolmogorov-Smirnov and Shapiro-Wilks tests. The nonparametric tests (Mann-Whitney, Wilcoxon, Friedman) were used for statistical analysis because of non-normality of the data and small sample size. Blood and milk BHBA were analysed by Mann-Whitney-U test to compare treatment and control groups including subgroups (with SCK or without SCK). Change of BCS from calving to postpartum day 30 and 60 was tested by Friedman test. Wilcoxon test was used for pairwise comparisons. Differences in BCS between group 1 and group 2 was evaluated by Mann-Whitney-U test. Incidence of the diseases in the groups was presented as percentage. Odds ratio (OR) was determined for each of diseases (for those with sufficient data for computation) in the groups. Mann-Whitney-U test is used to compare the average daily and weekly milk production between the groups and subgroups.

RESULTS

The average lactation numbers were 2.42±0.90 and 2.96±1.84 in the group 1 and 2 respectively (P>0.05). Blood and milk BHBA levels were not significantly different between group 1 and 2 at PW2 and PW4 (Table 2). The incidence of SCK in group 2 was 8% and 4% at PW2 and 4 in the blood test, it was 12% and 24% at PW2 and 4 in the milk test respectively (Table 3). However, SCK was not observed in group 1 in the blood and milk. The OR for SCK at PW4 in milk test was 5.68 times greater in group 2.

Table 2: BHBA concentrations (mean±standard error, mmol/L) and milk BHBA scores at postpartum week 2 and 4 and body condition scores (BCS, mean±standard error) at postpartum day 30 and 60 of treatment group (group 1, n=19) and control group (group 2, n=25).

Parameters		Group 1	Group 2	P
Blood BHBA	PW2	0.453±0.046	0.679±0.167	0.755
Blood BHBA	PW4	0.405±0.030	0.388±0.020	0.990
Milk BHBA*	PW2	0.463±0.043	1.333±0.580	0.488
Milk BHBA*	PW4	0.316±0.290	1.229±1.014	0.948
BCS	Calving	3.276±0.039[a]	3.248±0.039[a]	0.279
BCS	PPD 30	3.066±0.038[b]	3.010±0.049[b]	0.351
BCS	PPD 60	2.921±0.027[c]	2.850±0.086[c]	0.856
	P**	<0.0001	<0.0001	-

PW2: postpartum week 2. PW4: postpartum week 4. PPD30: postpartum day 30. PPD60: postpartum day 60. BHBA: blood beta-hydroxybutyric acid. BCS: body condition score. *Milk test strips indicate colours for 0, 50, 100, 200, 500, 1000 µmol/L of BHBA in the milk, which meet to BHBA scores 0, 0.5, 1.0, 2.0, 5.0 and 10.0 respectively. [a, b, c:] different letters refer to the significant difference within the group 1 and 2. **: refers BCS between calving, PPD30, PPD60

There was no significant difference between group 1 and group 2 concerning BCS at calving, including postcalving day 30 and 60 (Table 2), as well as in the subgroups (with and without SCK) (data not shown in tables). Almost all animals in the groups lost significantly BCS (P<0.01) on postcalving days 30 and 60 (Table 2).

Table 3: Incidence of subclinical ketosis, postpartum diseases and culling rate in treatment group (group 1) and control group (group 2) up to postpartum day 90.

Diseases	Postpartum	Group 1	Group 2
SCK (blood BHBA≥1.2 mmol/L)	Week 2	0.0%	8.0%
SCK (milk BHBA≥200 µmol/L)*	Week 2	0.0%	12.0%
SCK (blood BHBA≥1.2 mmol/L)	Week 4	0.0%	4.0%
SCK (milk BHBA≥200 µmol/L)*	Week 4	0.0%	24.0%[1]
Mastitis	90 days	10.5%	32.0%[2]
Metritis	90 days	5.3%	8.0%[3]
Laminitis	90 days	5.3%	4.0%[4]
Clinic ketosis	90 days	0.0%	4.0%
Culling rate	90 days	0.0%	12.0%
SCK in culled cows (blood)	Week 2	0.0%	0.0%
SCK in culled cows (milk)	Week 2	0.0%	33.3%
SCK in culled cows (blood)	Week 4	0.0%	33.3%
SCK in culled cows (milk)	Week 4	0.0%	66.7%

BHBA: betahydroxybutyric acid concentration. SCK: subclinical ketosis. *Milk test strips indicate colours for 0, 50, 100, 200, 500, 1000 µmol/L of BHBA in the milk, which meet to BHBA scores 0, 0.5, 1.0, 2.0, 5.0 and 10 respectively. SCK: subclinical ketosis. Odds ratio: [1]5.68, [2]4.00, [3]1.56, [4]0.75

Three cows in group 2 (12 %) and none of cows in group 1 were culled in 90 DIM. Cows were culled by the farm veterinarian at 73, 48, and 35 days postcalving due to udder problems, very low milk production and downer cow syndrome. Incidence of SCK based on the blood and milk tests on PW4 was 33.3 and 66.7% in the culled cows of group 2 respectively. No OR for culling

was generated in the statistical analysis with respect the SCK. The most common disease was mastitis in group 1 (10.5%) and group 2 (32%). OR respecting mastitis was 4.0 in group 2 with much higher incidence in 90 DIM. Metritis, laminitis and CK were observed at an incidence of 8%, 4%, and 4% in group 2 respectively, but without a significant OR (Table 3).

Table 4: Average daily milk yield (mean ± standard error, kg) in treatment group (group 1) and control group (group 2) and subgroups with and without SCK in the control group up to postpartum day 90.

Groups	n	Milk yield (kg)	P***
Group 1 (total)	19	33.92±1.65	
Group 2 (total)	25	30.69±2.49	>0.05
Group 2 with SCK*	6	19.06±6.44	<0.05
Group 2 without SCK	19	34.36±2.03	>0.05
Group 2 with SCK**	6	28.36±4.11	=0.07

SCK: subclinical ketosis (milk BHBA ≥200 µmol/L at postpartum week 4). *: Milk yield was taken zero as of culling day until 90 DIM. **: Milk yield was not included in the calculation after culling day. ***: P value refers in comparison with group 1 (treatment group)

Average daily and weekly milk production was presented in Table 4 and Figure 1. There was no significant difference between group 1 and group 2 concerning ADMP in 90 DIM. The number of SCK positive cows in group 2 was not enough at PPW2 to conduct a statistical comparison for milk yield. SCK positive cows in the milk testing at PW4 as a subgroup in group 2 had significantly reduced ADMY (19.06±6.44 kg) in 90 DIM (Table 4). The difference between the average daily and weekly milk production of group 1, 2 without SCK and group 2 with positive SCK was meaningfully different (P=0.026) if milk yield of culled cows with SCK tested in the milk or blood (n=2) was accounted for as zero from culling date to postcalving day 90th. The difference between average daily milk production of cows with positive SCK (28.36±4.11 kg) and without SCK (34.36±2.03) in group 2 was moderately significant (p=0.07) if the milk yield of culled cows in this group was not included in the calculation from culling date to postcalving day 90th.

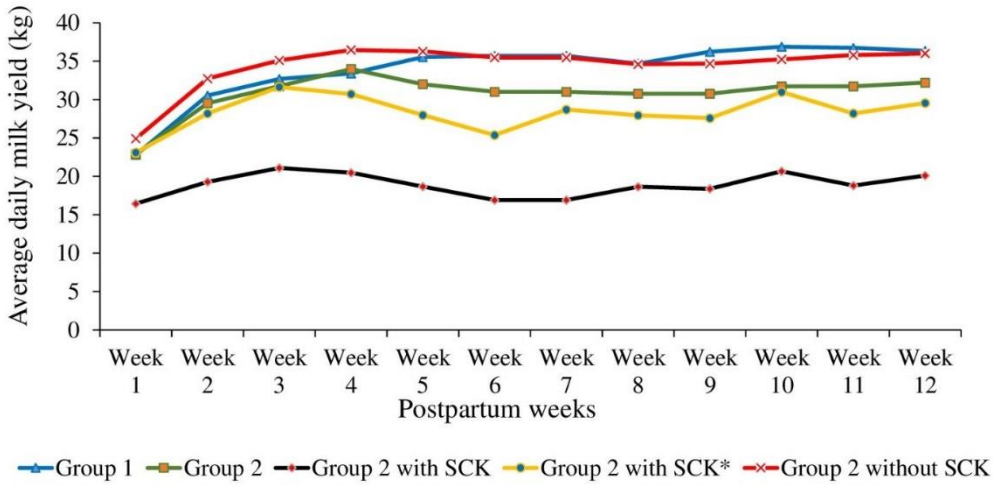

Figure 1: SCK: subclinical ketosis. Average daily milk production (kg) per week in the group 1 (treatment group), group 2 (control group with and without SCK) between postcalving week 1 to 12. *Group 2 with SCK: The milk production of culled cows with positive SCK in the control group was not included in the calculation after culling until to 90 DIM. Group 2 with SCK: The milk production of culled cows with positive SCK (n=2) in the control group was taken '0' in the rest of days after culling until to 90 DIM. SCK: cows with subclinical ketosis (milk BHBA ≥200 µmol/L at postpartum week 4). P<0.05 for the weeks 2 to 10 between group 1 (treatment group) and group 2 (control group) with SCK.

DISCUSSION

In the present study, blood and milk BHBA testing time points were the most prevalent period after calving and in line with previous reports in dairy cows (Brunner et al., 2018; McArt et al., 2012; Suthar et al., 2013). The cut-points for milk and blood BHBA for SCK were also in compromise with the previous reports (Benedet et al., 2019; Berge et al., 2014; Brunner et al., 2018; Gordon et al., 2017).

The present study did not find a significant effect of PPGT on average blood and milk BHBA at neither PW2 nor 4 that results were in line with the previous studies (Jeong et al., 2018). But, SCK was not observed in group 1 compared to group 2 in the present study, this was not reported by others because of the lack of classification of cows for SCK by the cut-points of BHBA. PG has been used for the treatment and control of SCK in dairy cows using different protocols (Gordon et al., 2017; Lomander et al., 2012; McArt et al., 2014; Zhang et al., 2020). However, there were contradictory and unsatisfactory results reported worldwide about the efficacy of PG in dairy cattle (Jeong et al., 2018; Lomander et al., 2012; Østergaard et al., 2020), although many dairy farms use preventive PG at calving in Türkiye. However, Gordon et al. (2017) stated that the PG treatment was beneficial in decreasing blood BHB concentrations in more severely affected animals with high blood BHBA and low glucose concentrations. That was a treatment regime with 2 more days of applications rather than a prevention. Oral drench of PG (400 ml) in lactating dairy cows (126 DIM) with positive energy balance reduced blood BHBA concentration within 2.5 h after the drenching, however blood BHBA concentrations increased in the 11 h post-treatment (Mikuła et al., 2020). PG drenching had short efficacy on the blood BHBA and treated cows were in 126 DIM and had positive energy balance, which is not comparable to the fresh cows treated preventively in the present study.

In the present study, the incidence of SCK observed in the blood and in the milk tests of group 2 looked a little lower than the previously reported prevalence in Turkey (Aksoy et al., 2022; Suthar et al., 2013; Şentürk et al., 2016; Uyarlar et al., 2018) and in the world (Brunner et al., 2018; Suthar et al., 2013). That might be a reason for the lack of efficacy of PPGT on the average milk and blood BHBA, or due to the dosage of PG. The prevalence of SCK was reported to be much higher when tested in the milk (Benedet et al., 2019; Berge et al., 2014) compared to blood test as reported by the present study as well. PPGT did not effect on BCS that was consistent with studies of Fonseca et al. (2004) and Jeong et al. (2018). However, it was inconsistent with the results of El-Kasrawy et al. (2020), who observed positive significant effect on BCS in 30 DIM at a much higher dosage of PG at pre- and postcalving.

Deniz et al. (2020) reported that cows with SCK have a significantly higher risk for displaced abomasum (DA), retained placenta (RP), milk fever (MF) and cystic ovarian (CO). McArt et al. (2011; 2014) reported that oral PG supported to cure hyperketonemia and reduced risks for DA. But, DA, RP, MF and CO were not observed in the present study. The study cows received oral calcium boluses at calving and had anionic feeding at close-up as standard protocol of the farm which can prevent from milk fever (Goff, 2008). Metritis and laminitis were observed both in group 1 and group 2 respectively, but without a significant odds ratio between groups. Suthar et al. (2013) reported 1.7 times higher risk for metritis and Brunner et al. (2018) reported 5.3 % incidence of metritis in SCK worldwide, and Uyarlar et al. (2018) reported 25 % incidence of metritis in SCK. The inconsistence with the literature might be due to different hyperketonemia incidence between the studies.

The most frequently observed postpartum disease was mastitis in group 1 and 2 thus group 2 cows had 4 times higher risk for mastitis compared to the cows in group 1. Similar results were reported by Uyarlar et al. (2018) in Türkiye. Suthar et al. (2013) did not find a significant correlation between mastitis and SCK. The high culling rate in group 2 and higher SCK incidence in culled cows were consisten with the previous studies (McArt et al., 2011; Uyarlar et al., 2018). Uyarlar et al. (2018) reported a 26.4 % culling incidence in cows with SCK. The results of the present study were similar with the previous reports. McArt et al. (2011) reported a reduction of culling rate in 30 DIM in cows treated with PG against SCK between 3-16 DIM. However, it was not a prevention study, rather a cure protocol of SCK. Although the result of the present study did not create a significant OR for culling rate and risk, the descriptive data showing a higher incidence of culling in group 2 is in line with the previously reported data.

The average daily and weekly milk production between group 1 and group 2 was not significantly different at 90 DIM. This was consistent with the data of Jenkins et al. (2015) and Jeong et al. (2018). Another study by Fonseca et al. (2004) indicated limited increased milk yield in cows treated with much higher oral PG dosages in the first 4 weeks of lactation, which was inconsistent with the results of our present study. A much higher dosage of PG (300 g, twice a day, from calving to 21 DIM) has slightly tended to increase the milk yield in 90 DIM (Lomander et al., 2012). Although a much higher dosage of PG used in those studies than in the present study, a limited increase in milk production was observed. Once the subgroups with and without SCK were created in group 2, a significant reduction in average daily and weekly milk production was observed in the SCK positive group. These results of the present study were in line with the previous studies (El-Kasrawy et al., 2020; McArt et al., 2014; Zhang et al., 2020), but many previous studies focused on the treatment of SCK rather than its prevention. SCK caused a significant loss of up to average 300 kg milk in 305 DIM (Deniz et al., 2020).

In terms of the overall effects of PPGT, the results of the present study are in line with others (Fonseca et al., 2004; Jenkins et al., 2015; Jeong et al., 2018; Østergaard et al., 2020). Other studies indicated also limited effects of PG, even no significant effect, but certain tendencies in the effects on the average milk production, BCS and postpartum health disorders were observed. Preventive treatment of all cows at 5 DIM with PG was the most cost-effective strategy when herd hyperketonemia incidence was >50% (McArt et al., 2014). No satisfactory effects were observed by PG application to balance the metabolic status and NEB in dairy cattle by others (Østergaard et al., 2020). Looking at the average worldwide prevalence (average 22–24%) as well as in the present study, the statement of McArt et al. (2014) that PPGT requires >50% incidence of hyperketonemia in the farm seems currently to be unrealistic.

CONCLUSION

In conclusion, PPGT at calving did not significantly affect the averages of blood and milk BHBA at PW2 and 4, BCS and ADMP. These results were in agreement with some previous studies that reported unfavourable results about PG effect. However, once the study cows were classified for SCK by blood and milk BHBA cut-off points, a clear effect of PPGT was observed on SCK incidence in association with postpartum health disorders and ADMP. Therefore, a risk assessment for the incidence of SCK should be performed in the respective farms based on cost-benefit calculations for PPGT in

advance. Consequently, a selective PPGT can be used in cows at risk or predisposed of SCK at calving or early postpartum rather than treating the entire population. PPGT in dairy cows can be an option and a next study hypothesis for small family business-dairy farming, in which professional tailor-made dairy management and continuous monitoring by veterinarians might be inadequate.

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Conflict of interest: The authors declare that they have no conflict of interest.

Ethical statement: This study was approved by the Muğla Sıtkı Koçman University Animal Experiments Local Ethics Committee (23.09.2021/34-21). In addition, the authors declared that Research and Publication Ethical rules were fully followed.

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