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Evaluation of Dietary L-Carnitine Supplementation during the Last Trimester of Pregnancy in Pregnancy Toxemia-Susceptible Goats: An Observational Field Study

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HIGHLIGHTS

- Addition of L-carnitine at a dosage of 100 mg/kg reduces blood NEFA concentration.
- L-carnitine supplementation at 100 mg/kg maintains stable blood BHBA levels.
- L-carnitine supplementation does not have a significant impact on body condition score.
- L-carnitine dietary supplementation may be useful for pregnancy management in goats.

Abstract: L-carnitine, an increasingly vital compound in livestock nutrition, plays a pivotal role in facilitating the β-oxidation of fatty acids. This study aimed to investigate the impacts of L-carnitine supplementation, administered at varying doses, on pregnancy toxemia susceptible goats. A total of 150 goats underwent estrus synchronization, natural mating, and pregnancy confirmation. Among these, 90 goats carrying multiple fetuses were categorized into three groups on the 100th day of pregnancy, with their feed supplemented as follows: CAR50 (50 mg/kg of L-carnitine), CAR100 (100 mg/kg of L-carnitine), and CON (control without L-carnitine). Subsequently, blood samples were collected from 15 randomly selected goats from each group on days 100, 115, 130, and 145 of pregnancy to quantify serum levels of β-HBA (beta-hydroxybutyrate) and NEFA (non-esterified fatty acids), alongside glucose levels. Dietary supplementation of L-carnitine did not exert a significant impact on blood glucose levels in the CAR50 and CAR100 groups, in comparison to the CON group, during the third trimester of pregnancy ($P>0.05$). Nevertheless, serum NEFA levels exhibited a noteworthy reduction in the CAR50 and CAR100 groups compared to the CON group on day 145 ($P<0.01$). Furthermore, no substantial fluctuations in mean NEFA and β-HBA levels were observed in the CAR100

group between days 100 and 145 of gestation (P>0.05). The body condition score exhibited consistent maintenance both within and between groups (P>0.05). To conclude, this study underscores the efficacy of dietary supplementation with L-carnitine in mitigating ketone and NEFA levels in pregnant goats, particularly when administered at a dosage of 100 mg/kg. Consequently, the integration of a standardized quantity of L-carnitine into the diet holds the potential to serve as a valuable preventive strategy for goats susceptible to pregnancy toxemia.

Keywords: Pregnancy toxemia; L-carnitine; goat; NEFA, β-HBA.

INTRODUCTION

In small ruminants late gestation and post-partum period have huge demand of energy [1]. The energy requirements of a pregnant goat in the late gestation are greater than that in early gestation, and significantly higher in the event of multiple pregnancies [2]. The requirement of energy or glucose required for fetal growth cannot be met with only carbohydrates. Therefore; body reserves of fat tissues start to mobilize to meet the energy demands of conceptus. The mobilization of fat generates non-esterified fatty acids (NEFAs) which are accumulated in the liver. It is indicated that the blood NEFA levels increase as the energy requirement increases. NEFAs accumulated in the liver are partly used as an energy resource, albeit remaining portion is converted into toxic ketone bodies namely β-hydroxybutyric acid (β-HBA), acetoacetic acid and acetone. All these byproducts increase the concentration of ketone bodies in body fluids (blood, milk, urine) in addition to hypoglycemia [3,4]. Such a condition in small ruminants is referred to as pregnancy toxemia or ketosis in small ruminants. Body condition score (BCS) serves as a pivotal indicator of an animal's nutritional status and physiological well-being. The animals having poor (≤2) or very high (≤4) body condition score (BCS) and aged 2 to 4 years are more prone to metabolic disorders. Moreover, high-yielding breeds are susceptible to disease, as they bear multiple fetuses and have high milk yield [5]. While conclusive evidence is lacking, certain genetic lines or families may exhibit increased susceptibility to the disease [6]. Ismail and coauthors [7] have reported a higher incidence of subclinical ketosis in Damascus goats compared to Baladi goats, suggesting a potential genetic predisposition, which may include a higher rate of multiple pregnancies.

The consequences of untreated pregnancy toxemia are dire resulting in an alarming 80% fatality rate among affected cases [6]. The efficacy of treatment varies based on the severity of the condition, further complicating the situation. Moreover, offspring born to toxemic goats exhibit an alarmingly low survival rate [8]. Therefore, prevention of pregnancy toxemia may be seen as a better strategy. The primary strategy in preventing pregnancy toxemia is undoubtedly management that ensures proper and adequate nutrition of pregnant animals [9]. In addition, feed additives such as L-carnitine, niacin, methionine, propylene glycol, sodium propionate, which have various roles in fat and glucose metabolism, have also been used as measures of prophylaxis [10-12]. Carnitine, a small vitamin-like amino acid, has been proposed to prevent ketosis in many species [10,13,14]. In past studies, L-carnitine has been used as a ruminal and abomasal infusion [15], subcutaneous [10], and intravenous injection [16], feed additive [17] or oral drench [18]. The majority of current routes of administration are invasive compared to oral consumption. In feeding studies, a completely randomized design with a 2×2 factorial arrangement is generally applied. Although the preventive efficacy of L-carnitine is well documented [10,14,17,19-23], the recommended practice requires an extra effort and time, as individual handling of each animal makes it impractical at herd level. In this study, goats tend to pregnancy toxemia were fed a diet supplemented with L-carnitine, a method that did not require individual handling of each animal. This study delves into an innovative approach—incorporating L-carnitine into the diet of goats susceptible to pregnancy toxemia. We hypothesized that L-carnitine at two different doses levels in a high caloric ration in the last trimester of pregnancy would help to increase serum glucose levels, reduce β-HBA and NEFA levels. The effects of L-carnitine on energy metabolism were determined via laboratory evaluation of serum metabolites and clinical evaluation of BCS in goats that have previously experienced pregnancy toxemia. Thus, it was aimed to reveal the applicability of this method in the management of pregnancy period.

MATERIAL AND METHODS

The study was conducted at a goat farm situated in the Gaziantep province of Turkey, an important choice for its specific geographical coordinates at latitude 37°10´45" N and longitude 36°44´10" E. Prior to conducting the experiments, ethical approval was obtained from the Ethical Committee of Mustafa Kemal University, Hatay, Turkey, under the reference number 2017/5-7

Animals and Study Design

In the study, female goats aged 3-5 years, having at least one birth, and body weights of 45-60 kg were used. The animals used in this study were members of a herd that had a multiple pregnancy rate of 83% during the previous breeding season experienced pregnancy toxemia-related losses despite receiving treatment. The goats were evaluated as members of a herd susceptible to pregnancy toxemia, taking into account their previous season's condition and possible genetic traits. Fluorogestone acetate (FGA) offers a strategic approach to synchronize estrus cycles and optimize breeding efficiency in goat herds. A total of 150 goats were synchronized with 20 mg FGA impregnated vaginal sponges (Chronogest Cr, Intervet, Istanbul, Turkey) in the breeding season (Early August). The sponges were inserted into to the vagina using a specialized speculum and kept for 9 days. The administration of 0.075 mg d-cloprostenol (Senkrodin®, Vetaş Turkey) was performed at the time of sponge removal. Estrus in goats was detected by five teasers rams for one hour each in the each morning and evening from the 12th hours of sponge removal. Goats in estrus were separated from the herd and mated with fertile rams.

Pregnancy examinations of goats were performed trans-abdominally using a real-time ultrasound device (Falco, PieMedica, Maastricht, Netherlands) with 6-8 MHz probe at 50 days of pregnancy. According to the results of the pregnancy examinations, 90 goats carrying multiple fetuses were randomly allocated into three equal groups on 100th day of pregnancy. 50 mg/kg L-carnitine (Carnipass®, Lonza Ltd., Switzerland) was supplemented to the concentrate feed of goats in the first group (CAR50) and 100 mg/kg to the feed of goats in the second group (CAR100) until parturition regardless of consumption. The third group was remained as control group (CON) and no supplementation was made (0 mg/kg L-carnitine). During this period, the goats were fed with concentrate having 16% crude protein, 2.56% ether extract, 12% crude fiber, and 2800 Kcal/kg metabolizable energy and good quality roughage (Table 1). Fig (1 kg/animal/day) and mixture of barley straw and meadow grass (1.2 kg/animal/day) were given as roughage. Roughage values were 46.28% ADF and 66.50% NDF. Water and mineral blocks were supplied ad libitum.

Table 1. The content of the concentrated feed mixture

Ingredients	**%**
Barley	38
Oat	15
Corn	9
Molasses	5
Sunflower meal	31
Limestone	1,4
Salt	0,5
Vitamin mineral premix*	0,1

*Each kilogram of premix contains 10 000 000 IU A vit, 2 500 000 IU D3 vit, 25 g E vit, 50 g Mn, 50 g Fe, 50 g Zn, 15 g Cu, 0.8 g I, 0.15 g, Co, 0.20 g Se

Blood Samples and Analyzes

Fifteen goats were randomly chosen from each group and tag numbers were recorded. Blood samples were collected from jugular vein 3 hours after the morning feeding. Samples were collected at multiple time points: before the addition of L-carnitine (day 100 of pregnancy) and then at 15, 30 and 45 days after the addition of L-carnitine (corresponding to day 115, 130 and 145 of pregnancy, respectively). Serum samples were obtained by centrifuging the blood samples at 5000 rpm for 10 minutes. Serum samples were stored at -20°C until further analysis. Blood glucose, β-HBA and NEFA levels were measured in the serum samples. The measurements were performed spectrophotometrically using an automatic biochemistry analyzer (RX Monaco, Randox Laboratories Ltd., UK). Commercial kits (GL8319 for glucose, Ranbut RB1008 for β-HBA, and FA 115 for NEFA, Randox Laboratories Ltd., UK) were used to analyze the levels of glucose, β-HBA, and NEFA in the serum samples.

Monitoring of Pregnancy Toxemia

Since the study was a field study for the prevention of pregnancy toxemia in herd, pregnancy toxemia was not induced in any of the goats. However, the disease, which could still occur, was followed up by observing common clinical symptoms (anorexia, lying down, lethargy, low head, convulsions and blindness) from the 100th day of pregnancy. In addition, serum analytes were also evaluated for the follow-up of pregnancy toxemia. β-HBA concentration higher than 0.8 mmol/L was evaluated as pregnancy toxemia.

Similarly, NEFA concentration >0.6 mmol/L, which is the critical level for pregnancy toxemia in serum samples, was evaluated.

Evaluation of Body Condition Score

Body condition was scored on groups by the same practitioner according to Mitchell [24] with a 4-point scale (1-4) scoring system and recorded on days 100 and 145 of pregnancy.

Statistical Analysis

All the statistical procedures were performed in a computer based statistical software package (Version 20.0, SPSS Inc., Chicago, IL, US) and RStudio, an open source software. To perform the statistical analysis, the following packages were loaded in RStudio: ggplot2, ggpubr, tidyverse, multcomp, and rstatix. Data were analyzed for significant changes in serum glucose, β-HBA, and NEFA levels of goats in response to supplementation of L-carnitine and sampling days. Wilcoxon rank-sum test or Mann-Whitney U test, depending on the data distribution were used. BCS, β-HBA and NEFA individual assessment of animals with high concentrations were compared analyzed using Pearson chi-square analysis.

RESULTS

NEFA changes between day 100 and 145 of pregnancy were significant in the CAR50 (P<0.05) and CON (P<0.001) groups (Figure 1). Blood NEFA levels were lower on day 130 and 145 in the CAR50 and CAR100 groups compared to the CON group although L-carnitine did not show statistical differences from the CON group until the 130th day of pregnancy (P>0.05). The CON group had the highest NEFA levels (0.74±0.16 mmol/L), while supplementation of L-carnitine significantly reduced NEFA levels in both the CAR50 (0.23±0.05 mmol/L) and CAR100 (0.25±0.06 mmol/L) groups (P<0.001) at day145 of pregnancy (Figure 1).

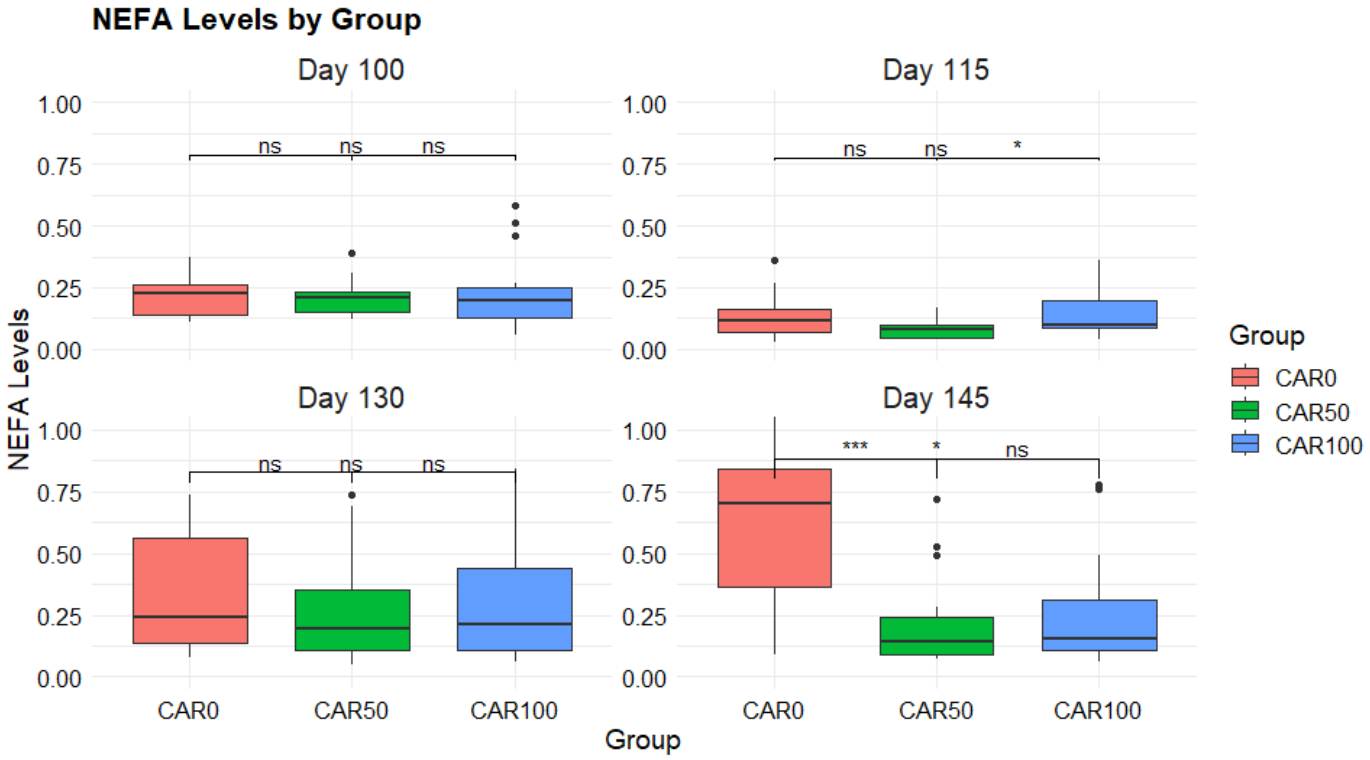

Figure 1. Blood NEFA levels measured at different days of pregnancy for two levels of carnitine supplementation. The x-axis represents the groups, where "CAR50" and "CAR100" indicate different levels of carnitine supplementation and “CAR0" as control group. The y-axis represents the NEFA levels. Each boxplot corresponds to a specific day of pregnancy (Day 100, 115, 130 and 145), indicated by the facet labels. The boxplots show the distribution of NEFA levels within each group and day. The significance labels above the boxplots indicate the statistical comparisons between groups (P<0.05), denoted by asterisks (*).

The blood ketone levels increased along with the advancement of pregnancy from 100th to 145th day in all the groups. The groups are evaluated within themselves, blood β-HBA changes between the day 100

and 145 of pregnancy was significant in CAR50 (P<0.001) and CON (P<0.05) group while not significant in the CAR100 (P>0.05). The highest ketone level (1.51 mmol/L) was obtained in the CON group at 145th day (P>0.05), (Figure 2).

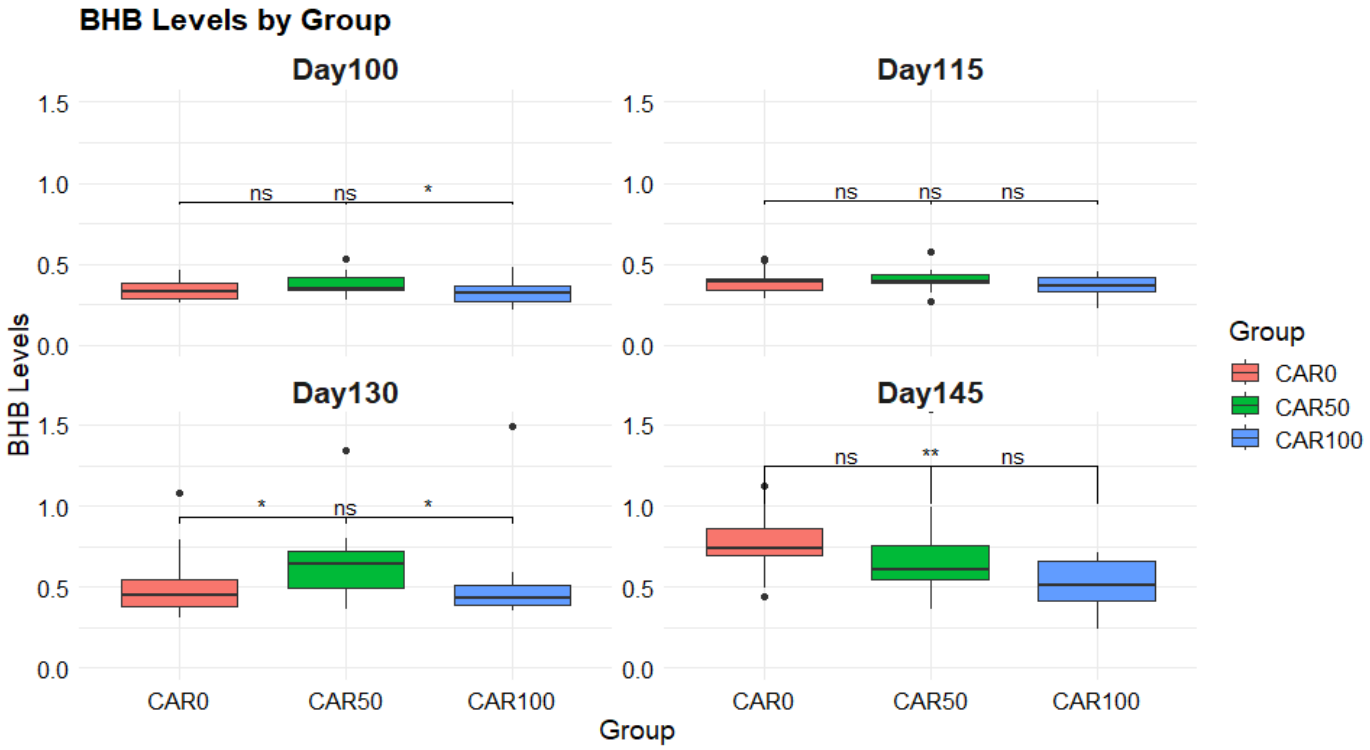

Figure 2. Blood ketone levels measured at different days of pregnancy for two levels of carnitine supplementation, as well as a control group. The x-axis represents the groups, where "CAR50" and "CAR100" indicate different levels of carnitine supplementation, and "CAR0" represents the control group. The y-axis represents the blood glucose levels. Each boxplot corresponds to a specific day of pregnancy (Day 100, 115, 130, and 145), indicated by the facet labels. The boxplots show the distribution of blood glucose levels within each group and day. The significance labels above the boxplots indicate the statistical comparisons between groups (P<0.05), denoted by asterisks (*).

None of the clinical symptoms of pregnancy toxemia were observed in animal in the study. Fetal death (abortion) or maternal death due to pregnancy toxemia did not occur. However, the rate of occurrence of pregnancy toxemia according to serum β-HBA level was highest in the CON group (33.33%, P>0.05). Similarly, the number of animals whose NEFA concentration exceeded the threshold value was highest in the CON group (53.33%, P<0.05), (Table 2).

Table 2. Pregnancy toxemia ratio according to serum metabolites in groups

(%, x/n)	CAR50	CAR100	CON	Total	P
β-HBA[1]	26,66 (4/15)	6,66 (1/15)	33,33 (5/15)	22 (10/45)	0,188
At 145[th] dop*	100 (4/4)	0,00 (0/1)	80 (4/5)	17,77 (8/10)	
NEFA[2]	6,66[a] (1/15)	13,33[a] (2/15)	53,33[b] (8/15)	24 (11/45)	0,006
At 145[th] dop*	0,00 (0/1)	50,00 (1/2)	50,00 (4/8)	45,45 (5/11)	
β-HBA[1] & NEFA[2]	6,66 (1/15)	6,66 (1/15)	26,66 (4/15)	40 (6/15)	0,177

[1]>0,8 mmol/L, [2]>0,6 mmol/L., *dop: Day of pregnancy. Different superscripts in same line show significant differences (P<0.05).

While the glucose level was different between the CAR50 and CAR100 groups on days 115 and 145 of the study, both groups were same with CON group. The highest glucose level on the sample days was obtained in the CAR100 group (P<0.05).Changes in glucose levels according to gestational days within groups were significant in all three groups (Figure 3).

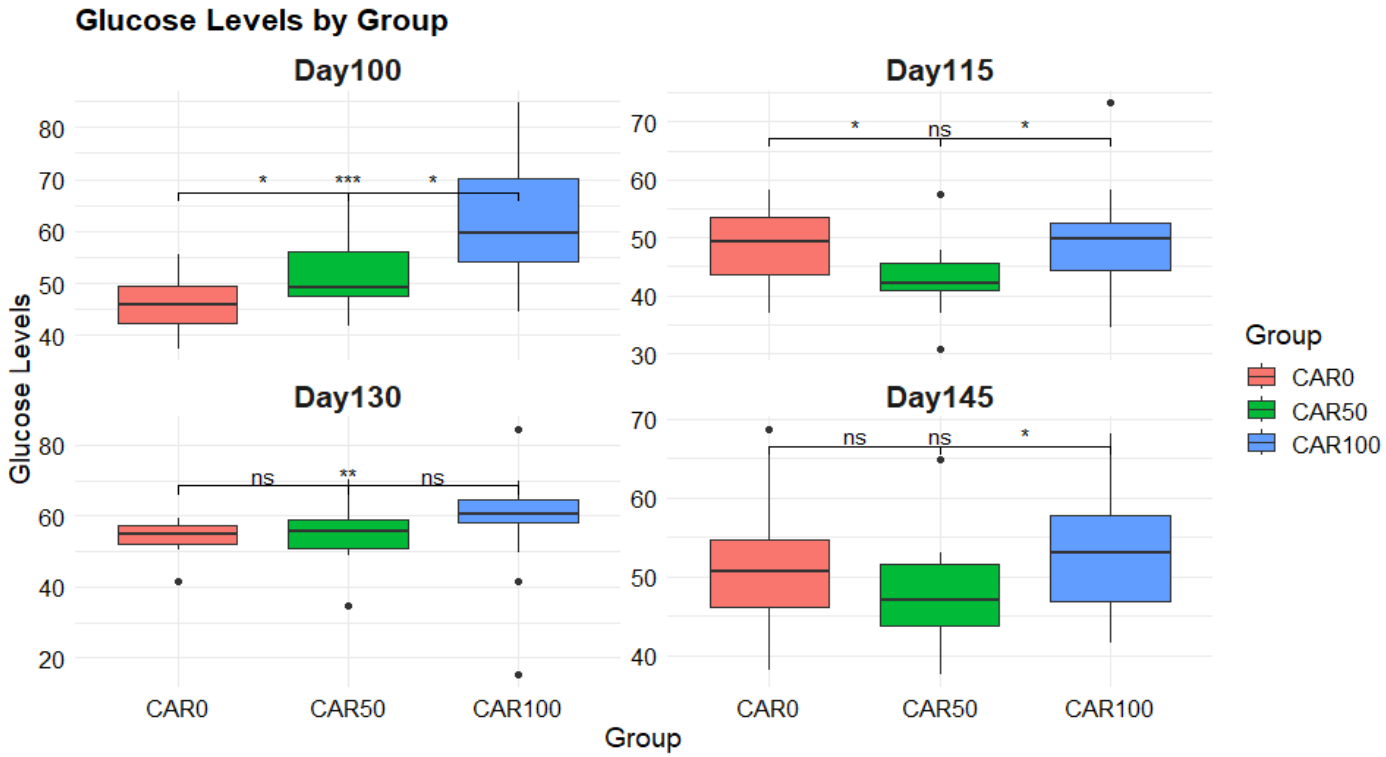

Figure 3. Blood glucose levels measured at different days of pregnancy for two levels of carnitine supplementation, as well as a control group. The x-axis represents the groups, where "CAR50" and "CAR100" indicate different levels of carnitine supplementation, and "CAR0" represents the control group. The y-axis represents the blood glucose levels. Each boxplot corresponds to a specific day of pregnancy (Day 100, 115, 130, and 145), indicated by the facet labels. The boxplots show the distribution of blood glucose levels within each group and day. The significance labels above the boxplots indicate the statistical comparisons between groups (P<0.05), denoted by asterisks (*).

L-carnitine supplementation did not improve BCS in the groups (P>0.05). BCS changes were not significant on different examination days in the same group (P>0.05). Also BCS values were not significant between the groups on the day 145 either (Table 3).

Table 3. Body condition scores of groups

Group	BCS		P
	Day 100	Day 145	
CAR50	2.5±0.21	2.1±0.17	NS
CAR100	2.73±0.20	2.5±0.22	NS
CON	3.0±0.20	2.63±0.21	NS
P	P<0.05	NS	

BCS: Body Condition Score, NS: Not significant, the difference were considered significant at P<0.05.

DISCUSSION

The findings of this study provide valuable insights into the potential benefits of L-carnitine supplementation in mitigating NEFA levels and protecting goats from pregnancy toxemia. During late pregnancy, goats rely on the mobilization of adipose tissue as an energy source [25], which leads to the release of NEFA, causing an imbalance in energy metabolism and the accumulation of ketone bodies or re-esterification into triglycerides [26]. In this study, the supplementation of L-carnitine demonstrated a significant impact on NEFA levels in goats during pregnancy. The results revealed that goats supplemented with L-carnitine (CAR50 and CAR100 groups) exhibited lower blood NEFA levels on days 130 and 145 of pregnancy compared to the CON group. Furthermore, as pregnancy progressed, blood ketone levels increased in all groups, with the CON group showing the highest level on day 145. This could explain why the proportion of animals exceeding the threshold NEFA concentration was highest in the CON group (53.33%, P<0.05), suggesting that L-carnitine supplementation plays a crucial role in modulating NEFA levels. Carnitine plays two important roles in this process: it facilitates the entry of long-chain fatty acids into

the mitochondria for oxidation and reduces acyl toxicity by converting fatty acids into carnitine esters [27]. Additionally, carnitine supplementation has been shown to increase hepatic glucose production through the β-oxidation of long-chain fatty acids [28]. Given that carnitine is more abundant in meat products compared to plants [29,30], ruminants like goats may benefit from exogenous carnitine supplementation during physiological processes. Previous studies have explored the effects of dietary L-carnitine supplementation in sows, sport horses, dairy cows, and dairy goats [17,19,21,23].

In this study, a fixed amount of L-carnitine was added to the feed of goats that had previously experienced pregnancy toxemia, with the intention of implementing the method throughout the entire herd. Although individual consumption of L-carnitine was not assessed, positive effects were observed, particularly at a dose of 100 mg/kg. Elevated NEFA levels during late pregnancy indicate increased lipolysis and negative energy balance, as body fat stores are mobilized to provide energy for the developing fetus [31]. However, high NEFA levels are also associated with pregnancy toxemia, a concerning condition. Our study measured NEFA levels on the 145th day of pregnancy in different groups. The CON group exhibited NEFA levels above the threshold (0.74±0.16 mmol/L), suggesting a potential risk of pregnancy toxemia. In contrast, the CAR50 and CAR100 groups showed lower NEFA levels (0.23±0.05 mmol/L and 0.25±0.06 mmol/L, respectively). Statistical analysis revealed significant changes in NEFA levels within the CAR50 and CON groups ($P<0.001$ and $P<0.05$, respectively), while the CAR100 group maintained stable NEFA levels ($P>0.05$). Interestingly, a higher proportion of goats in the CON group exceeded the threshold β-hydroxybutyrate (β-HBA) concentration (33.33%) compared to the CAR50 (26%) and CAR100 (6.6%) groups, although this difference was not statistically significant ($P>0.05$). Moreover, the CON group had the highest proportion of animals with elevated levels of both β-HBA and NEFA (26.66%), compared to the CAR50 (6.6%) and CAR100 (6.6%) groups. Within the CAR50 group, all goats with high serum NEFA levels also exhibited high β-HBA levels. However, in the CAR100 and CON groups, only half of the animals with elevated NEFA concentrations showed increased β-HBA levels. This discrepancy could be attributed to the timing of blood sampling, as previous research [32] has shown that NEFA levels increase earlier than β-HBA levels during fasting. Notably, in the CAR50 group, the rate of animals with NEFA >0.6 mmol/L was 6.66%.

It is important to note that goats require a blood glucose concentration of 30-60 mg/dL for normal physiological functions. Previous studies have highlighted the risk of pregnancy toxemia when blood glucose falls below this range [6]. However, pregnancy toxemia can lead to normoglycemia, hyperglycemia, or hypoglycemia [31,33]. In our study, the blood glucose levels of all goat groups remained above the threshold for normal physiological processes (30-60 mg/dL) (Figure 3). This result can be attributed to the high-energy diet (2800 Kcal/kg) provided to the flock. Although blood glucose levels were within the normal range, the presence of pregnancy toxemia in 10 animals based on β-HBA concentration (Table 2) indicates a potential glucose requirement that may not have been reflected in the measurements. Glucose resistance has been reported in toxemic pregnant goats with high body condition scores [31]. The normal blood glucose values observed in toxemic pregnant goats in our study may suggest the development of glucose intolerance, although further investigation is needed to confirm this. Studies in experimental animals have demonstrated that supplemental carnitine improves glucose tolerance in conditions such as insulin resistance, diabetes, and obesity [34]. Parenteral administration of L-carnitine in goats has been found to increase blood glucose levels [10]. However, in our study, blood glucose levels in the L-carnitine administration groups did not differ significantly from the control group ($P>0.05$) (Figure 3). Similar results were obtained by Molfino and coauthors [35] when evaluating the administration of L-carnitine with a hypocaloric diet. Although fasting glucose concentration was not affected by L-carnitine, it has been shown to reduce plasma insulin levels and improve insulin resistance in patients with Type 2 diabetes and impaired fasting blood sugar. Although blood glucose levels did not show significant changes in our study, considering the rates of pregnancy toxemia in the groups (26.66%, 6.66%, and 33.33% in CAR50, CAR100, and CON groups, respectively, Table 2), it can be speculated that glucose utilization may be increased in goats regularly consuming L-carnitine. Clinical symptoms of pregnancy toxemia in goats, such as shaky gait, muscle tremors, and depression, are typically observed when the β-HBA concentration exceeds 4 mmol/L [32]. Hypoglycemic brain damage is believed to contribute to the manifestation of these symptoms [36]. In our study, although the highest β-HBA concentration measured from toxemic animals in the CON group was 7.84 mmol/L, no clinical symptoms were observed. This can be attributed to the absence of hypoglycemia in any of the animals. However, considering that high β-HBA concentration can indicate past hypoglycemia, even if not reflected in the blood results, it is possible that some animals experienced undetected hypoglycemia that did not reach severe levels leading to irreversible nervous system damage.

The body condition score (BCS) is a subjective method used to assess the fat reserves and overall condition of live animals [37]. It is often considered an indicator of nutritional status [38]. High BCS during

pregnancy can lead to complications like pregnancy toxemia, placental retention, and dystocia, while low BCS decreases offspring survival rates [5]. In our study, we did not observe any significant differences in BCS changes among the groups (P>0.05) (Table 3). Since no severe clinical signs of pregnancy toxemia were observed in any of the goats, significant average BCS changes were not expected in the groups. Although L-carnitine showed positive effects on the serum profile, it did not have a noticeable impact on BCS, which aligns with findings in prepartum cows [13]. Mehaba and coauthors [17] also reported no effect of L-carnitine supplementation on feed consumption in dairy goats. The lack of an increase in feed consumption in our study may have contributed to the observed results. However, without evaluating individual feed consumption, it is difficult to draw definitive conclusions on this matter. Despite similar declines in BCS across the groups, the CON group exhibited significantly higher circulating NEFA concentration (P<0.05), suggesting increased utilization of NEFA in the carnitine-supplemented groups. To comprehensively examine the effects of L-carnitine on BCS changes, variables such as feed consumption and weight change should be considered. The findings of the present study provide valuable insights into the potential benefits of L-carnitine supplementation in mitigating NEFA levels and protecting goats from pregnancy toxemia. Further research is warranted to explore individual feed consumption, weight change, and glucose utilization in goats consuming L-carnitine to better understand its comprehensive effects on energy metabolism and body condition.

CONCLUSION

This study found that adding L-carnitine to the diet in the last trimester of pregnancy kept serum NEFA and β-HBA levels lower in goats. Accordingly, supplementing the ration with L-carnitine, along with a high-calorie diet, may be considered as a protective strategy in herds with a history of pregnancy toxemia. Adding L-carnitine to the diet can be considered as a part of pregnancy management that requires less labor and time, has little effect on animal welfare, and has low costs compared to veterinary medications and injection treatments.

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