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Incidence, diagnosis and treatment of pregnancy toxaemia in Hassan sheep

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Abstract
The study was carried out to record the incidence, diagnosis, treatment for pregnancy toxaemia (PT) and its effect on reproductive parameters in Hassan ewes. The ewes in their last 4-6 weeks of pregnancy with BHBA levels ≥0.8 mmol/L were diagnosed to have PT and were randomly divided into 3 groups. Ewes in group 1 (n=6) did not receive any supplementation and served as positive control, group 2 (n=9) were daily administered (p.o) with 25 mL of GLYCOW, group 3 (n=8) were daily supplemented with 100 g of broken maize and healthy pregnant ewe with BHBA <0.8 mmol/L (group 4; n=6) were taken as negative control for comparison. The ewes were monitored up to lambing and periparturient complications, birth weight and growth rate of lambs were recorded. The incidence of PT recorded was 15.33%. Mean blood glucose level among the groups did not vary significantly during the course of treatment but significant decrease in mean BHBA levels was recorded in group 2 and 3. The BHBA decline was more pronounced and earlier in the group 2 compared to group 3. Decreased gestational length was observed in untreated PT ewes compared to that of group 2, 3 and 4. Periparturient complications were higher in untreated ewes and no complications in healthy ewes. It is concluded that pregnancy toxaemia in Hassan ewes needs to be detected at the right time and treated promptly to minimize the financial loss to the shepherds.

Keywords: Hassan ewes, pregnancy toxaemia, BHBA, Glycow

Introduction
Pregnancy toxemia (ketosis) is the common metabolic disorder of sheep during late pregnancy and early lactation. It frequently occurs in the last 4-6 weeks of pregnancy, resulting in considerable financial losses due to a high death rate in pregnant ewes and more prevalent in ewes carrying two or more lambs or in very fat ewes and also oversized singletons. As the pregnancy advances, the energy demands of the fetus increase. At the same time, the capacity of the ewes' rumen shrinks since developing fetus in the uterus occupies more space inside leaving less space for the rumen (Bickhardt *et al*., 1989; Drackley *et al*., 1989) [7, 9]. This combination prevents the ewe from getting enough energy from her diet. As a result, in order to supply energy for growing fetus, ewes will breakdown her own fat tissue, releasing harmful ketone bodies into bloodstream. When this occurs too rapidly, the ewe's body will be unable to eliminate the ketone bodies quickly enough, which leads to ketosis (pregnancy toxaemia). Ketosis can occur if the ewe is overweight because fat takes up space inside the sheep, leaving less area for the rumen to hold feed. Circumstances that prevent feed intake like storms, hauling or other illnesses can also cause this metabolic disorder (Freetly and Ferrell, 1998) [13].
Clinical symptoms in the affected ewe include initially lagging behind the rest of the flock, depressed, partial anorexia and reluctant or fail to move from approaching people. They may become recumbent within 2-4 days after noticing the clinical signs. Other important symptoms include teeth grinding, apparent blindness, muscle tremors, tachypnoea with or without grunting, constipation, reduced ruminal motility, fruity or sweat smell to the breath, and edema of distal extremities. Later, they become remarkably depressed to comatose, exhibit head pressing or star-gazing, unable to get up, dehydrated, and complete rumen atony (Rook, 2000) [33].
The estimation of blood glucose and beta hydroxy butyric acid (BHBA) levels plays very important role in early diagnosis of the condition (Lacetera *et al.*, 2001) [27]. If PT diagnosed in the early stages, medical treatment can be successful (Andrews, 1997; Sargison, 2007) [2, 35] and treatment in advance cases is usually unsuccessful (Marteniuk and Herdt, 1988) [29]. Reviewing pregnancy toxaemia in ewe is crucial to recognize and to avoid the predisposing

situation, to prevent and control the disease occurrence as well as to prevent production losses. Information about incidence of PT and its effect on production and reproduction in Hassan ewes was not documented earlier and hence, the current study was conducted with prior approval from the Institutional Animal Ethical Committee (VCH/IAEC/2022/34) for handling and maintaining welfare of study animals.

Materials and Methods

Design of the experiment

Based on the breeding records available in the Hassan sheep unit, AHP, Hassan the ewes were subjected to trans-abdominal ultrasonography for confirmation of pregnancy between June - December, 2022. The ewes in their last 4-6 weeks of pregnancy were subjected to blood glucose and BHBA estimation using Freestyle Optium-H Blood glucose and ketone monitoring system and appropriate strips (Abbott Laboratories, UK). Ewes with BHBA levels ≥0.8 mmol/L (subclinical pregnancy toxaemia) were randomly assigned into three groups. Ewes in Group 1 (n=6) did not receive any supplementation or treatment and served as positive control. Group 2 ewes were daily administered with Glycow commercial ketosis treatment preparation (Veteran Laboratories, Mandya, Karnataka) containing propylene glycol (160ml v/v), liquid glucose (25g w/v) and cobalt chloride (20mg w/v) 25mL p.o until BHBA reaches within physiological levels. In Group 3, ewes daily supplemented with an additional 100 g of broken maize until lambing. Daily blood glucose and BHBA levels of the study ewes were estimated before grazing for next three consecutive days or until their levels reached normal physiological levels. All the study ewes were closely observed for signs of parturition around the end of gestation and a total of 6 healthy pregnant ewes in their advanced gestation (Group 4) were also considered for comparison. Difficult births, stillbirths, birth of weak lambs, if any were recorded. Birth weight and weekly body weight for three consecutive weeks of each lamb was recorded to assess the growth rate of lambs in healthy, control and treated groups. Further, post parturient complications such as retained fetal membranes (RFM), metritis, if any found were recorded.

Blood BHBA, blood glucose, birth weight and weekly body weight of lambs were analysed by two-way ANOVA following Tukey's multiple comparison test using Graph pad Prism version 5.0. The values were represented by means±standard error and the differences were considered statistically significant at $P<0.05$.

Results and Discussion

Incidence

The incidence of pregnancy toxaemia (subclinical) in Hassan breed of ewes in the present study was found to be 15.33 percent. Similar prevalence rate of subclinical ketosis (14.86%) was reported by Gupta *et al.* (2008)[14] in Muzzafarnagri breed of sheep reared in organized farming system and 13.16 percent overall prevalence of subclinical ketosis was reported in Ballari, Kenguri, Deccani and Non-descript ewes by Basavanagouda (2021) [5]. However, lower prevalence (2.6 %) in Chios breed of sheep (Karagiannis *et al*., 2014) [24] and intensively reared small ruminants (1.6 - 7.1%) (Lima *et al*., 2016) [28] have been reported. Andrews *et al.* (1996) [3] reported higher prevalence which ranged from 31-41 percent and 20 percent in pantaneiro genetic group ewes reared in intensive system (Feijo *et al.,* (2016). Further, Kelay and Assefa (2018) [25] stated that prevalence of ketosis among the sheep vary with differences in management system, fecundity and rate of hepatic gluconeogenesis.

Association of parity with incidence

The association of pregnancy toxaemia with parity in the present study was ascertained and 78.26 percent in parous and 21.74 percent in nulliparous Hassan breed of ewes were documented. Similar results were recorded by Gupta *et al.* (2008) [14] as 16.66 percent in nulliparous and 83.33 percent in parous Muzzafarnagri breed ewes with PT. Usually the risk of PT is observed in older ewes during their second or subsequent pregnancies and low fecundity in maiden ewes is less prone to the disease, which increases up to third parity with concurrent disease or musculoskeletal issues restricting mobility and feed intake, as well as other variables affecting energy balance in late gestation (Rowe, 2014) [34]. Contrarily, it has been observed that early-parity animals are still growing and need nutrients for their own growth as well as the growth of the fetus, which causes a considerable decrease in glucose and a rise in NEFA in the last trimester in primiparous ewes. These changes in primiparous ewes are pronounced compared to multiparous ewes in the immediate pre-lambing to maintain the nutrient supply for the growing fetus and their continued body growth (Wathes *et al.*, 2007; Singh *et al.*, 2022) [36, 40].

Blood glucose levels

In the present study the mean blood glucose levels (mg/dL) in Hassan ewes with PT on the day of diagnosis was 63.96±3.35 (range: 21-80) with 72.67±2.81, 61.00±6.98 and 60.75±4.88 in Group 1, 2 and 3 ewes, respectively. There was non-significant increase in blood glucose level from day 1 (70.78±5.525 and 65.50±5.14 mg/dL) to day 3 of treatment (79.56±2.91 and 74.38±3.51) in Group 2 and Group 3 compared to untreated control group (73.00±2.55 to 73.50±2.08 mg/dL). Similar mean plasma glucose levels of 59.40±14.40 and 52.02±3.12 mg/dL in PT/ketotic ewes on the day of diagnosis was recorded by Duehlmeier *et al.* (2013)[10] and Henze *et al.* (1998) [18], respectively. Further, hypoglycemia was recorded only in 40 percent, normoglycemia in 40 percent and hyperglycemic in 20 percent of ketotic ewes and the plasma glucose values showed high variations in the group of affected animals compared with the healthy ones. Similarly, Souto *et al.* (2019) [37] recorded mean blood glucose level (mg/dL) as 97±2.9 in Santa Ines, Dorper, and mixed breed ewes with pregnancy toxaemia where they have reported normoglycemia (68.94±7.2 mg/dL) and hyperglycemia (132.12±30.96 mg/dL) in 82.9 percent and only 17.10 percent ewes were hypoglycemic (43.74±5.22 mg/dL).

Sargison (2007) [35] opined that ewes with PT typically have progressive hypoglycemia, but blood glucose levels can fluctuate and are not consistently correlated with the severity of clinical symptoms or the prognosis. Cal-Pereyra *et al.* (2015) [8] recorded an increase in blood glucose level following treatment in experimentally induced PT in Corriedale ewes in the similar fashion of present study. In pregnant ewes, high level of blood glucose concentration observed as most common finding due to the stress condition resulted in high level of cortisol and further pathologic increases in cortisol are associated with maternal and fetal

morbidities with cortisol having adverse effect on maternal glucose homeostasis (Keller-Wood *et al*., 2014) [26]. A decreased capacity of the sheep to metabolize glucose at the end of gestation, with rising glycemic levels likely due to increased insulin resistance in peripheral tissues and a small proportion of sheep with hypoglycemic and another proportion of affected animals with normoglycemia do suffer from PT (Henze *et al*., 1998; Pereira *et al*., 2010) [18, 32] and the similar trend of blood glucose level in Hassan ewes with PT has been observed in this study.

Herdt and Emery (1992) [19] recorded increase in blood glucose levels within 12 h of treatment in response to propylene glycol administration. Propylene glycol is primarily absorbed intact from the rumen directly at a rate of 40 percent/h, reaches its peak blood level within 30 minutes of ingestion and reaches its peak blood glucose transformation via pyruvate conversion at around 4 h later. In the group 3 ewes of the present study supplemented with broken maize, there was slow increase in blood glucose level compared to group 2 because the broken maize must be broken down by the ruminal microorganisms and should get converted into volatile fatty acids in particular propionic acid (Fahey and Berger, 1993) [12]. Thus produced propionic acid must then be absorbed at the level of the ruminal papillae before being partially transformed into lactate in the rumen wall and both being converted into glucose in the liver via gluconeogenesis. About 18 - 42 percent of maize starch may escape rumen breakdown and get digested in the small intestine (Orskov, 1986)[31] but only 30 to 35 percent of the glucose produced by intestinal starch digestion could be found in the portal vein (Huntington and Reynolds, 1986) [21].

Blood BHBA levels

The mean blood BHBA level (mmol/L) on the day of diagnosis in ewes with subclinical pregnancy toxaemia (SCK) was 0.92±0.01, 0.88±0.04 and 0.80±0.00 in Group1, 2 and 3, respectively with overall mean of 0.86±0.03 in the present study. Mean blood BHBA level on day 2 of treatment in Group 1, 2 and 3 was 0.90±0.04, 0.54±0.04 and 0.69±0.04, respectively whereas on day 3, it was 0.92±0.01, 0.48±0.05 and 0.51±0.04 mmol/L, in Group 1, 2 and 3, respectively indicated that the treatment resulted in decrease in BHBA level. Similar BHBA levels have been reported by Marutsova and Marutsova (2018) [30] during last two weeks prior to lambing in Lacaune and Mouton-charollais sheep with SCK as 1.11 mmol/L and Vijayanand *et al*. (2021) [39] as 1.3±0.05 mmol/L in small ruminants with PT. Higher mean blood BHBA levels in ketotic sheep was reported as 3.47±0.22 mmol/L by Henze *et al.* (1998) [18], 4.82±0.27 mmol/L by Vasava *et al.* (2016) [38]. The values of BHBA decreased in treated groups (G1 and G2) within 24 h of treatment, and this decline was significant and earlier in the group supplemented with GLYCOW (G2) (**day 0**: 0.88±0.04 vs. **day 1**: 0.60±0.06 vs. **day 2**: 0.54±0.04 vs. **day 3**: 0.48±0.05 mmol/L) compared to group supplemented with broken maize (G3) (**day 0**: 0.80±0.00 vs. **day 1**: 0.74±0.07 vs. **day 2**: 0.69±0.04 vs. **day 3**: 0.51±0.04 mmol/L). Cal-Pereyra *et al.* (2015) [8] reported similar trend of decline in blood BHBA level in glycerol + propylene glycol (2.6 vs. 1.1 vs. 0.7 mmol/L) and supplemented with two daily intakes of cracked corn (2.5 vs. 1.7 vs. 1.5 mmol/L). The decrease was quicker and sharper in ewes treated with propylene glycol compared to the ewes supplemented with broken maize and the concentration of blood BHBA in the former remained significantly lower throughout the study period.

The lack of dietary energy intake leads to insufficient substrate available for ruminal production of the glucose precursor (propionate) resulting in a period of negative energy balance. This situation predisposes to high degree of lipid mobilization, subsequent production of NEFAs and their β-oxidation generating substantial amounts of ketone bodies resulting in excess BHBA levels (Andrews *et al*., 1996; Andrews, 1997; Hefnawy *et al.*, 2010) [2, 3, 17]. Moreover, ketone bodies produced by the liver are utilized by other tissues, and ketosis could be caused by either underuse or overproduction. The rise is caused by a decrease in pregnant females' ability to utilize BHBA, which has a number of negative consequences on energy balance and glucose metabolism, promoting the development of PT, particularly in sheep with twin/multiple pregnancies (Harmeyer and Schlumbohm, 2006) [15]. Propylene glycol increases concentration of pyruvate and oxaloacetate production via pyruvate carboxylase. In response to the concentration of intra-mitochondrial citrate increased oxaloacetate to form malonyl-CoA, a potent transformation suppressor of fatty acids into mitochondria. Thus, ketone body production decrease and propylene glycol increases insulin: glucagon ratio ameliorating the ketosis (Aiello *et al.*, 1984; Jesse *et al.*, 1986; Herdt and Emery, 1992) [1, 19, 22].

Gestational length

Mean gestational length in Hassan breed of sheep with PT in Group 1, Group 2, Group 3 and in healthy (Group 4) was 146.3±0.95, 149.0±1.11, 149.5±0.38 and 150.3±0.33 days, respectively. Similar gestation period of 145.75±0.35 days was reported by Barbagianni *et al.* (2015)[4] in Chios crossbred ewes suffered from PT. However, Abreu-Palermo *et al.* (2021) reported that the mean gestation length (148.06±0.54 days) in Corriedale breed of ewes with subclinical PT (induced) did not vary when compared with healthy ewes. The reduced gestational length in the present study might be attributed to the maternal under-nutrition and effect of ketones which caused the fetal hypothalamo-pituitary-adrenocortical axis stimulation (Edwards and McMillen, 2002) [11].

Lambs birth weight

In the present study, mean lamb birth weight in Group 1 (positive control), Group 2 (GLYCOW), Group 3 (broken maize) and Group 4 (healthy) was 2.42±0.07, 2.62±0.16, 2.13±0.09 and 3.17±0.13 Kgs, respectively. Barbagianni *et al.* (2015) [4] recorded median body weight of lambs in Chios cross breed of ewes with PT was 3.5 kg (2.0-5.3 kg) and 4.0 kg (2.7-5.9 kg) in ewes of control group. Duehlmeier *et al.* (2013)[10] reported lower birth weight of lamb born to German black headed mutton and Finnish Landrace breed of PT ewes (2.2±0.2 kg) as compared to that of healthy ewes (2.6±0.6 kg). About 60 percent of fetal growth occurs in the last few weeks of gestation and about 33 - 36 percent of the blood glucose of the dam is directed into the feto-placental unit. But in starved ewes or ewes with PT, only 17 percent of the glucose is available through the umbilical vein (Hay *et al.*, 1983) [16]. Continuous availability of glucose becomes most important for fetal growth and is the main nutrient that crosses the placenta, followed by amino acids (Herrera *et al*., 1985) [20] which are highly required for the fetal development. A very little amount of BHBA may be transported to the fetus and

this ketone body becomes an important energy source for the placenta, but fetus/es unable to utilize (Battaglia and Meschia, 1988) [6]. The ewes' BHBA and birth bodyweight of lambs are negatively correlated and ewes with pregnancy toxaemia usually produce lambs with lower birth weight (Andrews, 1997) [2].

Nonetheless, Edwards and Mc Millan (2002)[11] in their study found no significant effect of restricted nutrition either during periconceptional or gestational period on fetal weight in Australian Border-Licester-cross Merino ewes with singleton fetus.

Lambs' weekly body weight

Weekly body weight of lambs born to ewes suffered from PT and healthy ewes was taken and mean body weight (Kgs) in Group 1 (positive control), Group 2 (GLYCOW), Group 3 (broken maize) and Group 4 (healthy) was 3.07±0.048, 3.60±0.30, 3.00±0.20 and 4.10±0.14 in first week, 3.55±0.06, 4.08±0.29, 3.60±0.40 and 5.25±0.13 in second week and 4.25±0.03, 4.90±0.28, 4.25±0.35 and 6.07±0.24 in third week, respectively. There is limitation of literature to compare the results of the present study. However, the reduced colostrum and milk production in ewes that had pregnancy toxaemia results in a lack of nutrients for lambs resulting in reduced growth rate of lambs (Andrews, 1997; Karagiannis *et al.*, 2018) [2, 23] which is consistent with the present study.

Periparturient complications

The Periparturient complications observed were dystocia, stillbirth and birth of weakling in Hassan breed of ewes. In ewes of group 1 (2/6; 33.33 %) followed by Group 3 (1/9; 12.5 %) and Group 2 (1/8; 11.11 %) and no periparturient complications observed in Group 4 (healthy ewes). Periparturient complications was observed in 4 out of 23 ewes with PT (17.40 %) which included two stillborn (50 %), one dystocia (25 %) and one weakling (25 %). A high incidence of dystocia has been reported in the treated ewes whether parturition is induced or not (Boileau, 2008). Many either fail to enter active labour (stage II parturition) or develop ringwomb. Karagiannis *et al.* (2014) [24] recorded 20.80 percent Chios ewes with PT which developed at least one periparturient health disorder *viz*., metritis in 8.2 percent, retained fetal membranes in 1.7 percent and mastitis in 4.8 percent. Barbagianni *et al.* (2015) [4] recorded higher periparturient complications in 50 percent of Chios crossbreed ewes with PT, 8 ewes had dystocia due to postural abnormality in 25 percent and expulsive deficiency in 75 percent with five dead foetuses and two weakling which died by the 2nd day of birth. Ewes with pregnancy toxaemia often develop expulsive deficiency as the consequence of primary uterine inertia, attributed the inadequate endocrinological mechanisms required for parturition, the impaired fetal HPA axis stimulation in growth-retarded fetuses consequent to the maternal under nutrition (Edwards and McMillen, 2002) [11] or to the shorter gestation length in the ewes with the PT (Barbagianni *et al.*, 2015) [4].

Reduced quantity of colostrum production in ewes suffered from PT also contributes to neonatal lamb mortality (Andrews, 1997) [2]. Keller-Wood *et al*. (2014) [26] has clearly suggested the adverse effect of elevated cortisol level in pregnant ewes which affects the maternal glucose homeostasis and that continued maternal stress / excessive cortisol secretion contribute to maternal gestational diabetes, consequent fetal pathophysiology and perinatal mortality. Perinatal mortality in offspring of ewes with pregnancy toxaemia has been attributed to the effect of intrauterine fetal growth retardation due to the consequent reduced energy availability in such ewes (Barbagianni *et al.*, 2015) [4].

Conflict of Interest

There is no clash of interest among the authors.

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Conclusion

It was concluded that about 15.33 percent of Hassan ewes in their advanced pregnancy suffered subclinical PT and they had shorter gestational length with higher periparturient problems. The lambs born to PT ewes had low birth weight and lower weekly weight gain. Hence, prophylactic measures should be in place to minimize the economic loss to the shepherds due to lamb mortality, lower lamb growth rate including ewe infertility problems.

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