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Article Review

Pregnancy Toxemia in Ewes

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ABSTRACT

Pregnancy toxemia (PT), is a metabolic illness brought on by a negative energy balance that affects sheep and goats, which commonly called pregnancy disease or twinning disease. Impaired metabolism of lipids and carbohydrates is a hallmark of this illness. Pregnancy toxemia, which can cause maternal mortality, abortion, or early delivery, is especially dangerous for obese and multiparous ewes. The disease's root cause is increased energy needs during pregnancy combined with insufficient nourishment to fulfill metabolic demands. Liver lipidosis is the result of excessive lipid metabolism and ketosis, which are brought on by this negative energy balance. Pregnancy toxemia is chemically characterized by hypoglycemia and hyperketonemia which prevent the animal from maintaining an adequate energy balance. Therefore; supplying of high-energy grains and concentrates in the final month of pregnancy, and adhere to appropriate management may be recommended to minimize and avoid livestock losses. An immediate and accurate diagnosis usually increases the chance of subsequent treatment and prevention. Preventing losses in sheep production requires an understanding of the disease's etiology, pathophysiology, prevention, and treatment.

INTRODUCTION

Twin-bearing ewes develop pregnancy toxemia, a metabolic disease with a high death rate, towards the end of the gestational period **(Schlumbohm and Harmeyer, 2008)**. Pregnancy toxemia, also known as 'twin-lamb' disease, caused by an abnormal carbohydrates and lipid metabolism, that occurs in the later stage of pregnancy **(Brozos et al. 2011).** These negative energy balances toward the end of pregnancy are believed to be the main cause of pregnancy toxemia and development since the energy needed throughout pregnancy is significantly higher than the energy generated by feeding **(Pough. 2002)**. Hypoglycemia, fat mobilization, ketonemia, and ketonuria are the results of a phase of negative energy balance and poor gluconeogenesis that precedes pregnancy toxemia **(Rook 2000)**. It is characterized by hypoglycemia, low liver glycogen level, elevated blood ketone bodies(hyperketonemia) and increased plasma free fatty acids **(Van**

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Saun, 2000). Multiple pregnancies in ewes, low-quality energy intake, low dietary energy, hereditary variables, obesity, poor bodily condition or high parasite load, and inactivity are risk factors **(Rook, 2000).** Crossbred ewes with multiple pregnancies have a much higher risk of developing ketosis **(Olfati, and Moghaddam 2013).** In addition, this can also be observed in malnourished sheep that have only one large fetus **(Bani Isail et al. 2008).**

The disease has a 5–20% incidence rate, and in animals that are left untreated, the fatality rate can exceed 80%. Furthermore, 40% of ewes pass away even with a rigorous treatment plan **(Rook 2000).**

Review methodology:
Using Google, a comprehensive analysis of English-language publications from 1976 to the present was carried out. All articles on the subject, regardless of the journals and publishers, are also included. Toxemia, pregnancy, sheep, ewes, ketosis, hypoglycemia, diagnosis, and prevention were among the search terms used.

Clinical findings:
Separation from the group, failure to come up for feeding in pastoral animals, or standing close to the trough with the group of sheep but not eating in housed animals are early signs of pregnancy toxemia. Other symptoms include altered mental state and apparent blindness, which is characterized by an alert bearing but a reluctance to move. Additionally, they lie down, feel sluggish, and exhibit appetite loss.

Ewes that are affected walk unsteadily, seem lethargic, and don't seem afraid of people or dogs. Blindness is frequently the result, followed by convulsions, dyspnea, and tooth grinding. Should it be compelled to move, it will bump into things and then crush its head against the obstruction. Numerous ewe sheep that are impacted stay in feeders and sip water all day long **(Radostits et al. 2006).**

In later stages, there are periods of more severe anxious sensations and noticeable tiredness but these are less common and are easily missed. In these episodes, head muscles tremors cause lips twitching, jaws champing and salivation **(Rook 2000).** Alongside these, the cervical muscles contract in a cog-wheel pattern, causing the head to dorsiflex or lateralize before moving in a circle. Usually, the entire body experiences muscle trembling, causing the ewe to collapse in convulsions. After every seizure, the ewe calmly lies down and then rises normally, but she remains blind. There is a noticeable lethargy in between convulsions, which can be accompanied by pressure on the head, strange postures, such as tilting the limbs or lifting the chin (the "stargazing" posture), poor coordination, and falling to the ground when trying to move **(Pough 2002).**

The ewe's breath may also have a pronounced ketone odor. After three to four days, affected ewes typically lie down and stay in a marked depression or coma for three to four more days.

Most cases occur one to three weeks before lambing. More severe illness and a higher chance of death are linked to symptoms that appear before the 140th day of pregnancy **(Kahn 2005).**

Lesions:
An enlarged adrenal gland and a pale, bloated, and friable fatty liver are typical findings. Additionally, the sick ewe frequently has many fetuses in her uterus **(Bradford, 1996)**. A premortal death is indicated if the fetuses are in a stage of decomposition. Serous atrophy of the kidney and heart fat may give the appearance of starvation in extremely thin ewes **(Kahn 2005).**

According to **Ermilio and Smith (2011),** in situations of pregnancy toxemia, the doe's liver may swell and turn yellow as a result of fat infiltrating the hepatocytes, which impairs liver function.

Diagnosis:

Depression, anorexia, weakness, a stumbling stride, apparent blindness, a lying-down coma, and death are all signs of ketonemia. **(Al-Qudah, 2011).** The presence of pregnant toxemia in ewes can only be verified by ele-

vated plasma ketone body concentrations, such as β-HB, because of the lack of distinct clinical signs **(Duehlmeier et al. 2011**). Blood study is necessary to confirm the diagnosis of pregnant toxemia, which is based on clinical signs and history **(Wastney et al. 1983).** Hypoglycemia, high urine ketone levels, elevated BHBA levels, and often hyperkalemia and hypocalcaemia as a result of severe ketoacidosis are among the laboratory results in ill ewes. Pregnancy toxemia and low CSF glucose levels are both indicated by low blood glucose levels **(Scott et al. 1995)**. However, hypoglycemia is not a permanent finding. Normal glucose levels are present in up to 40% of cases while hyperglycemia are reported in up to 20%. This led to the hypothesis that whereas hyperglycemia would suggest that the fetuses are dead, hypoglycemia might suggest that they are alive. **Wastney et al. (1983)** indicated that the prenatal inhibitory impact on hepatic gluconeogenesis is reversed by fetal death, which causes hyperglycemia. **(Smith, and Sherman 1994),** mentioned that final cases had a noticeable hyperglycemia. BHBA is a more accurate measure of disease severity than blood glucose levels when the diagnosis needs to be confirmed.

Elevated non-esterified fatty acids can potentially be a sign of likely hepatic lipidosis, which impairs liver function **(Bickhardt, et al. 1989).**

Blood's Biochemical Parameters:

Blood tests performed in a biochemical laboratory can diagnose pregnancy toxemia. Early and precise diagnosis of pregnancy toxemia is essential for dairy sheep breeders. When diseases are accurately and promptly diagnosed, they are typically easier to treat and avoid. Dead goats have substantially lower blood pH, pCO2 values, HCO3-levels, and blood K+ concentrations than living goats **(Lima et al. 2016).** One reason for hypokalemia was that the goats weren't eating, which meant they weren't getting enough K from their food. In goats, increased quantities of unmeasured strong ions may accompany acidosis, which is frequently linked to pregnancy toxemia (**Gomez et al. 2020).** Pregnancy toxemia can also result in hypocalcemia **(Iqbal, et al. 2022).** 7.13 mg/dL is the ideal calcium threshold for clinical pregnancy toxemia. At the farm level, measuring the blood calcium and BHBA levels of the afflicted animals is the only reliable method of distinguishing between the two illnesses **(Brozos et al. 2011).** Pregnant ewes' early postnatal metabolic markers are highly predictive of the lambs' outcomes **(Gomez et al. 2020).** The best predictors of pregnancy toxicity are lactate dehydrogenase, potassium, creatinine, fructosamine, and malondialdehyde **(Iqbal et al. 2022).** When blood L-lactate and blood gas pCO2 levels rise and lamb blood pH and blood base excess decrease, the results are worse **(Andrade, et al. 2019).** Thyroid hormone alterations during the postpartum period, as well as their role in the pathophysiology of ketosis and metabolic response to negative energy balance, have been thoroughly investigated in ruminants (**Meikle et al. 2004;** and **Huszenicza et al. 2006).** Additionally, a study examining the metabolic and endocrine features of pregnant toxemia revealed that females with the condition had lower T4 and T3 levels, hypoglycemia, hyperketonemia, and hypoinsulinemia compared to healthy animals **(Prohaczik et al. 2009).**

Pregnant toxemic ewes usually have blood glucose levels less than 2 mMol/L. Of the sheep with pregnant toxemia, 55.0% had hypoglycemia, 15.0% had hyperglycemia, and 30.0% had normal blood glucose levels **(Iqbal et al. 2022).** Although glucose serves as the main metabolic fuel and is necessary for organ function, its stringent homeostatic regulation makes it an insensitive energy indicator **(Rayan et al. 2019).** As the condition worsens, ewes become more sedentary and their blood glucose levels rise, but in the early stages, hypoglycemia serves as a diagnostic tool **(Constable et al. 2017).** The most reliable markers of both clinical and subclinical pregnancy toxemia are fructosamine and NEFA. The average blood glucose during the previous one to three weeks is displayed by fructosamine **(Malkan et al. 2015).** Fructosamine is a good diagnostic and prognostic biomarker since sheep have a 98% chance of dying when their levels fall below 0.02 mMol/L. It is possible to raise the NEFA concentration above 0.4 mMol/L. Hypoglycemia is the cause of elevated NEFA levels because it causes an excessive

mobilization of adipose tissue **(Iqbal et al. 2022).**

Although they are not specific, changes in serum components' levels and patterns can be diagnostically significant in metabolic disorders. Serum components are the most widely used biochemical markers that are regularly examined to diagnose or track disease activity **(Moghaddam and Olfati, 2012).** Serum protein electrophoresis has been shown by numerous researchers to be useful for the preliminary evaluation of a range of clinical or pathological situations in animals **(Gojnic et al. 2004; Camacho et al. 2005).**

The mediators linked to the metabolic alterations in ewes with pregnant toxemia have been the subject of numerous investigations **(Scott et al. 1995; Harmeyer and Schlumbohm, 2006). Yarim and Ciftci (2009)** revealed that pre-eclamptic pregnant sheep had a considerably lower serum albumin content than uncomplicated pregnant ewes. It is difficult to quantify how ewes' reproductive state affects their serum values. Research on how the various stages of reproduction affect serum parameter readings also produced contradictory results **(Ramin et al. 2005; Harmeyer and Schlumbohm, 2006; Yarim and Ciftci, 2009).** Consequently, the authors of those studies suggest that more animal science research be done in the future with an emphasis on the crucial connection between blood chemistry and pregnancy toxemia diagnosis in sheep at various gestational stages.

Pregnant toxemic ewes may have elevated LDH activity as a result of liver, skeletal, and cardiac muscle injury **(Iqbal, et al. 2022).** Damage to the liver is indicated by elevated AST and GGT activity **(Souto, et al. 2019).** Goats with pregnancy toxemia may exhibit myocardial injury, which raises the troponin and creatine kinase myocardial band levels noticeably **(Souza, et al. 2020).** Consequently, the diagnosis of ovine pregnancy toxemia may benefit from specific blood chemistry levels.

Elevated urine ketone concentrations or elevated serum BHBA levels are indicators of pregnancy toxemia. When BHBA plasma levels in clinically normal sheep reach 0.6 to 0.7 mMol/L, ketonuria may develop. Ketone bodies in urine are measured using commercial qualitative test strips; a positive result denotes ketonuria **(Cal-Pereyra, et al. 2015)**. One prodromal stage of pregnancy toxicity is ketonuria. The gold standard for diagnosing ketosis is laboratory measurement of blood BHBA level **(Oetzel 2004)**. Superoxide radicals produced by ketones can subsequently transform into hydroxyl radicals. By starting the breakdown of membrane phospholipids and causing the buildup of lipid peroxidation end products, these free radicals cause cytotoxicity. While normal cells can detoxify superoxide radicals using antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), glutathione reductase, and catalase (CAT), these products are known to cross-link membrane components, resulting in changes in membrane permeability and lipid organization, as well as cellular dysfunction and membrane damage. These enzymes help maintain the intracellular concentrations of reduced glutathione and NADPH, which are essential for the optimal function of the antioxidant defense system **(Jain et al. 2006).**

Treatment of Pregnancy Toxemia:

Acidosis, increased blood and urine ketones, and hypoglycemia are common symptoms of pregnancy toxemia. As a result, liver protection, detoxification, and glucose supplements are typically the cornerstones of treatment.

For late-stage pregnant toxemia, there is no proven cure. The flock as a whole should be treated, and the ewe who is already unconscious should be put down **(Duehlmeier, et al. 2013).**

Pregnancy Toxemia Prevention:

Pregnancy toxemia may usually be avoided by striking a balance between the fetus's increased needs during late gestation and the mother's nutritional needs. By managing ewes well, breeders can avoid pregnancy toxemia. First, enhancing the rearing environment and preventing sheep stress might be advantageous **(Sejian et al. 2021).** Second, ewes can avoid

accumulating too much fat or losing weight by altering their food **(Kasimanickam, 2016).** In addition to providing protein, vitamins, minerals, and other nutrients, the feed for pregnant ewes should also consider the sensible combination of different nutrients and promptly alter the feed's contents based on the ewes' weight. During the second two months of pregnancy, the breeder can give 250 g of concentrate daily; two weeks prior to delivery, this amount can be increased to 300–400 g/day **(Qing 2021).** Third, it can be beneficial to feed single and multiparous ewes separately **(Lacetera et al. 2001).** Fourth, keeping an eye on ewes' physiological and biochemical markers throughout pregnancy can help breeders detect pregnancy toxemia early **(Silva et al., 2022).** Furthermore, tracking changes in insulin, glucose, and thyroid hormones is a crucial method for evaluating anabolic or catabolic adaptations in dairy cows during pregnancy and lactation **(Fazio et al. 2022).**

CONCLUSION

A metabolic condition known as pregnancy toxemia causes significant mortality and financial costs for farmers. Giving the mother the right nourishment can be the single most crucial element in preventing pregnancy toxemia. The breakdown of the ewe's glucose homeostasis mechanism in response to the fetus's increased nutritional needs during pregnancy is believed to be the cause of pregnancy toxemia. To understand the mechanism of pregnancy toxemia in sheep and investigate the possible role of diagnosis, therapy, and prevention of pregnancy toxemia in ewes at aberrant metabolic states, more research is needed. Veterinarians can utilize this information to promote healthy reproduction and reduce financial losses in the sheep farming sector.

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