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Causes, Control and Prevention Methods of Pregnancy Toxemia in Ewe: A Review

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ABSTRACT

Pregnancy toxemia, also known as ovine ketosis, twin-lamb disease or gestational toxemia is a metabolic disease affecting pregnant ewes. The objective of this review is to highlight possible causes and predisposing conditions of pregnancy toxemia in ewe and to indicate successful control and prevention methods of the disease. English articles published from 1983 to date was searched with Google using toxemia, pregnancy, ewe, treatment, prevention, ketosis and diagnosis as key terms. The increased requirement for energy during pregnancy, accompanied by inadequate nutrition to meet metabolic requirement is the underlying cause of the disease. This negative energy balance initiates the onset of excessive lipid metabolism and ketosis, and eventually causes hepatic lipidosis. An excess of ketone bodies can occur in both poor and good conditioned sheep and in fact, excessively fat ewes can be more prone to pregnancy toxemia. Moreover, conditions that interrupt feed intake, such as storms, hauling or other diseases can also induce this metabolic disease. Affected sheep exhibit weakness and depression, usually within the last six weeks of pregnancy. It has seen more often in older ewes and those carrying multiple fetuses. Pregnancy toxemia is almost never observed in replacement ewe-lambs or yearlings lambing for the first time. If untreated, the disease progresses, causing neurological signs and eventually death. Therefore, Understanding the causes, pathogenesis, prevention and treatment of this disease is important in preventing production loss in sheep farming operations.

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INTRODUCTION

Among domestic farm animals metabolic diseases achieve the greatest importance in dairy cows, pregnant does and ewes. In other species these disease occur only sporadically. If the continued nutritional demand of pregnancy is exacerbated by an inadequate diet in the dry period, the incidence of metabolic disease increases. The effect of pregnancy is particularly important in ewes, especially those caring more than one lamb [1].

Pregnancy toxemia, also known as ketosis, is the most commonly occurring metabolic disease of sheep and goats that occurs in late pregnancy. It commonly occurs in the last 6 weeks of gestation which causes significant economic losses and high mortality rate in pregnant ewes. It is most prevalent in ewes carrying two or more lambs or in very fat ewes. Ketosis is caused by a disturbance in carbohydrate usage in the animal [2]. As ewe's pregnancy progresses, the energy demands of her body increase. At the same time, the capacity of her rumen shrinks since her growing lambs in the uterus take up more and more space inside leaving less space for the rumen [2, 3]. This combination can result in the ewe not receiving sufficient energy, through her diet. As a result she will have to resort to breaking down her own body tissues, usually fat, in order to provide energy for her growing lambs, thus releasing ketones (a toxic byproduct of fat breakdown) into her bloodstream. When this occurs too rapidly, the ewe's body cannot detoxify the ketones fast enough and ketosis or pregnancy toxemia results. Ketosis can also occur when the ewe is too fat since fat also takes up room inside of the sheep resulting in less space for the rumen to hold feed. Additionally, conditions that interrupt feed intake, such as storms, hauling or other diseases, can also induce this metabolic disease [4].

Ewes with ketosis are lethargic and have a poor appetite for the last 1 to 2 weeks of pregnancy. They also tend to have poor muscle control and balance. A classic symptom is sweet-smelling (ketotic) breath. Sheep may also grind their teeth. As the disease progresses, the neurological systems become compromised due to lack of glucose. Hence, encephalopathy results from depressed glucose metabolism in the brain [5]. Blindness, stargazing, tremors, aimless walking and ataxia are seen and eventually the ewes become comatose and are unable to rise. Death usually follows within a few days [6].

The determination of blood glucose and beta hydroxyl butyric acid (BHBA) concentrations is very important for early diagnosis [7]. If pregnancy toxemia is diagnosed in the early stages, medical treatment can be successful [5, 6]. But the treatment of advanced pregnancy toxemia is usually unsuccessful [8]. In general Pregnancy toxemia, once develop result in stop eating, nervous sign, blindness, and eventually death so reviewing Pregnancy Toxemia in ewe important to know and avoid the predisposing condition, to prevent and control the disease occurrence besides to prevent production losses. The objective of this review is therefore to highlight possible causes, predisposing conditions of pregnancy toxemia successful control and prevention methods of pregnancy toxemia in ewe.

METHODS

A systematic review of English articles published from 1983 to date was conducted using Google. All articles related to the topic was also included without any preference to types of journals and publishers. Search terms included were toxemia, pregnancy, Sheep, ewe, treatment, prevention, ketosis and diagnosis.

RESULTS AND DISCUSSION

Etiology

The cause of pregnancy toxemia is a metabolic disturbance of Carbohydrate or sugar and fats during the final stage of pregnancy [9]. This disturbance is caused by low glucose concentration in the blood and excessive breakdown of body fat to compensate glucose deficiency. Ketones are the toxic by-products produced during this rapid breakdown of fat and it is possible to test for their presence in the ewe's urine. Inadequate nutrition during the last 6 weeks of pregnancy is the primary cause of low blood sugar as ewes cannot consume enough feed or energy to meet the demands of their growing fetuses. This is because approximately 70% of fetal growth occurs during the last 6 weeks of pregnancy [10].

Over-conditioned (BCS 4 or more) ewes are also susceptible to pregnancy toxemia because of fat in their abdominal region. In such fat ewes there isn't enough room in the gut for the ewes to eat sufficiently and there is an excessive fat resource for breakdown resulting in ketosis. Under-conditioned (BCS 2 or less) ewes are also susceptible because they cannot eat enough to meet their own nutritional needs, let alone the added burden of developing fetuses [4].

Epidemiology

Occurrence. It occurs in all parts of the world. With the drive to increase lambing percentages and margins dependent on feed costs, particularly in intensively farmed lowland flocks, the problem has become widespread. The disease is rarely seen under extensive production systems [5]. In part, this is because the breeds of sheep used in intensive farming are more likely to bear twins or triplets. Since the disease most often affects ewes/does pregnant with twins or triplets, it is characterized by low blood sugar. In contrast, sheep breeds in extensive grazing systems commonly bear single lambs and significant outbreaks of pregnancy toxemia are uncommon except where there is drought or poor pasture management. In general, the incidence of pregnancy toxemia is greater in ewes with more than one fetus during the last 6 weeks of gestation [1].

Many farmers will be faced with a few cases annually, but in certain years up to 40% of ewes in a flock may be affected [5]. Death occurs in 2-10 days in about 80% of the cases. The incidence in a flock varies with the nature and severity of the nutritional deprivation and the proportion of the flock at risk. It can be very high in starvation Pregnancy toxemia, whereas fat ewe pregnancy toxemia is generally of sporadic occurrence. In outbreaks that follow management procedures or other stressors, clinical disease is not manifested until 48 hours and afterwards new cases will develop over several days. The natural incidence in intensively farmed sheep is approximately 2% of pregnant ewes but where there are sever managemental deficiencies of the

disease, it may affect the majority of late pregnant ewes. The case fatality is high unless treatment is initiated early in the clinical course. It causes 100% ewe mortality and High neonatal mortality in untreated case. Even with early treatment case fatality can be high [1].

Risk factors

Pregnancy. The primary predisposing cause of pregnancy toxemia is inadequate nutrition during late gestation, usually due to insufficient energy density of the ration and decreased rumen capacity as a result of fetal growth. The disease occurs only in ewes in the last 6 weeks of pregnancy, usually during the last month, with the peak incidence in the last 2 weeks of pregnancy. This is because in the last 6 weeks of gestation the requirement of metabolizable energy rises dramatically. It occurs primarily in ewes carrying twin lambs because twin pregnancy increases susceptibility of ewes to hypoglycemic stress and Pregnancy toxemia. For example, ewes carrying twins require 1.9 times more energy than ewes with singles and ewes with triple fetuses require 2.3 times more energy than ewes with singles [11]. Pregnancy toxemia may also affect ewes bearing a single large lamb [12].

Body condition. Poor body condition, old age, obesity and low body weight are other predisposing factors for the onset of the disease. During late gestation, in the presence of obesity, the abdominal space is filled with accumulated fat and an expanding uterus. Because of lack of rumen space, these females have difficulty in consuming enough feedstuff to satisfy their energy requirements [13]. Ewes with poor body condition also cannot eat enough to meet their own nutritional needs and the energy requirement of their fetuses [4]. This is because susceptible thin ewes are chronically offered with inadequate ration, and in the face of increasingly insufficient energy to meet increasing fetal demands, the ewe mobilizes more body fat with resultant ketone body production and hepatic lipidosis [11].

Diseases. Presence of other diseases like; foot rot, foot abscess and parasites can also influence the onset of pregnancy toxemia. Because such conditions acutely curtail feed intake [14] so that the animal becomes in negative energy balance.

Environmental stress. Environmental stressors such as cold weather and rain increase the energy demand of the pregnant ewe so that induces stress (acute) syndrome [15]. Transportation, shearing, crutching or drenching also cause stress and may contribute to the onset of the disease.

Parity. Clinical cases are typically limited to older goats and ewes during their second or subsequent pregnancies. The disease is uncommon in maiden ewes because of their low fecundity and increases in prevalence up to parity three [10].

Breed. In sheep and goats, pregnancy toxemia is much more common in highly prolific selected breeds [16]. Breed differences largely reflect differences in fecundity and differences in management systems. For instance, the disease is more common in British lowland breeds and their crosses than the Merino. On the other hand, British hill breeds are traditionally believed to be more resistant to the development of pregnancy toxemia in the face of nutritional deprivation of the ewe but resistance is achieved at the expense of lamb birth weight and has the penalty of higher neonatal mortality. There are however, differences in the susceptibility of individual sheep that appears to be related to differences in rates of hepatic gluconeogenesis [1].

Pathology

Pathogenesis. In late gestation, the liver increases gluconeogenesis to facilitate glucose availability to the fetuses. Each fetus requires 30–40 g of glucose/day in late gestation, which represents a significant percentage of the ewe's glucose production and which is preferentially directed to supporting the fetuses rather than the ewe. This is because approximately 70% of fetal growth takes place in the last 6 weeks of pregnancy. Mobilization of fat stores is increased in late gestation as a method of assuring adequate energy in the face of increased demands of the developing fetuses and impending lactation. However, in a negative energy balance, this increased mobilization may overwhelm the liver's capacity and result in hepatic lipidosis with subsequent impairment of function [11]. Ewes with hepatic lipidosis have an ineffective gluconeogenic response to the continued, preferential demands for glucose by the growing fetuses resulting in hypoglycemia, more lipid mobilization and accumulation of ketone bodies and cortisol. 80% of ewes have a high plasma cortisol concentration. This could be the consequence of increased adrenal output or reduced excretion by the liver [17]. The reason for this predisposition is not known. Twin bearing ewes appear to have more difficulty in producing glucose and clearing ketone bodies, thus increasing their susceptibility to pregnancy toxemia. The subsequent disease and metabolic changes are associated with excessive lipid mobilization [8, 10].

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According to Sargison [6], Ketone bodies (BHBA and acetoacetate) are strong acids and their accumulation in the blood leads to metabolic acidosis. Schlumbohm and Harmeyer [18] revealed that high BHBA impairs glucose metabolism. This further suppresses endogenous glucose production and exaggerates the development of ketosis. Since hyperketonemia exerts several adverse effects, e.g. on energy balance and glucose metabolism it appears that the impairment of ketone bodies disposal in late pregnancy facilitates development of Pregnancy toxemia, especially in ewes carrying twins [19].

The disease manifests with an encephalopathy, believed to be a hypoglycemic encephalopathy resulting from hypoglycemia in the early stages of the disease. The encephalopathy and the disease are frequently not reversible unless treated in the early stages. The onset of clinical signs is always preceded by hypoglycemia and hyperketonemia, although the onset of signs is not related to minimum blood glucose or maximum ketone levels [20].

Lesions

Pale, swollen and friable fatty liver and enlarged adrenal glands are common findings. In addition, the uterus of the affected ewe usually has more than one fetus [21]. If fetuses are in a state of decomposition it indicates premortem death. Very thin ewes may appear starved with serous atrophy of the kidney and heart fat [11].

Clinical findings

The earliest signs of pregnancy toxemia are separation from the group, failure to come up for feeding in pastoral animals or standing near the trough with the group of sheep but not eating in housed animals, altered mental state and apparent blindness, which is manifested by an alert bearing but a disinclination to move. They also lie down, become sluggish and show a loss of appetite. Affected ewes walk unsteadily, appear dull and they show little fear of humans or dogs. Blindness often results and eventually there can be convulsions, grinding of the teeth and labored respiration. If it is forced to move, it blunders into objects and when an obstacle is encountered, presses against it with its head. Many affected ewes stand in water troughs all day and lap the water [1].

In later stages, marked drowsiness develops and episodes of more severe nervous signs occur but they may be infrequent and are easily missed. In these episodes, tremors of the muscles of the head cause twitching of the lips, champing of the jaws and salivation. These are accompanied by a cog-wheel type of clonic contraction of the cervical muscles causing dorsoflexion or lateral deviation of the head, followed by circling. The muscle tremor usually spreads to involve the whole body and the ewe falls with convulsions. The ewe lies quietly after each convulsion and rises normally afterwards but is still blind. In the periods between convulsions there is marked drowsiness which may be accompanied by head pressing, the assumption of abnormal postures including unusual positions of the limbs and elevation of the chin - the 'stargazing' posture - and in coordination and falling when attempting to walk. A smell of ketones may be detectable on the breath of the ewe. Affected ewes usually become recumbent in 3-4 days and remain in a state of profound depression or coma for a further 3-4 days. Most cases develop 1-3 weeks before lambing. Onset earlier than day 140 of gestation is associated with more severe disease and increased risk of mortality [11].

Diagnosis

The diagnosis of pregnancy toxemia is based on history and clinical findings but confirmatory diagnosis requires blood analysis [22]. Laboratory findings in individual ewes may include hypoglycemia**,** elevated urine ketone levels, elevated BHBA levels and frequently hypocalcaemia and hyperkalemia due to severe ketoacidosis. Low blood glucose level indicates pregnancy toxemia as well as CSF glucose level [20]. However, hypoglycemia is not a consistent finding. With up to 40% of cases having normal glucose levels while up to 20% having hyperglycemia. These gave rise to the idea that hypoglycemia might indicate that the fetuses are alive and hyperglycemia that the fetuses are dead. Wastney et al. [22] suggested that the hyperglycemia occurs because fetal death removes the suppressing effect of the fetus on hepatic gluconeogenesis [16], referred to the existence of a marked hyperglycemia in terminal cases. If the diagnosis needs further confirmation, BHBA is a more reliable indicator of disease severity than blood glucose levels. Non esterified fatty acids can also be elevated, indicating likely hepatic lipidosis resulting in impaired hepatic function [2, 8].

For an accurate diagnosis, a differential diagnosis is important to determine pregnancy toxemia from other disorders with similar signs such as hypocalcaemia or hypomagnesaemia. These can be differentiated based on clinical and laboratory findings. Typical signs and indications that differentiate pregnancy toxemia from hypocalcaemia includes: in pregnancy toxemia there is slow progression of the disease with death after 5-7 days where as in hypocalcaemia there is rapid progression of the disease with death after 6-24 hours. Elevation of the chin ('star-gazing') with slow progression to recumbence over 2-3 days after onset of initial signs is seen in pregnancy toxemia but during hypocalcaemia rapid progression to recumbence over 3-4 hours and sternal recumbence with the head stretched out and chin on the ground with legs folded beneath or stretched out behind the ewe is usual. In post-mortem examination liver is yellowish with a fine mottled appearance characteristic of pregnancy toxemia but there are usually no significant and characteristic observable post mortem findings in hypocalcaemia. In response to treatment in pregnancy toxemia, there is no response to dose rates of hypocalcaemia treatment with commercial calcium solutions. Usually poor and slow response to doses of glucose or energy with best responses seen if treated whilst ewes are still alert.

Treatment

Successful treatment of pregnancy toxemia requires early detection and steps to quickly meet the energy (glucose) needs of the affected ewe. Therapy requires the correction of fluid, electrolytes and acid-base disturbances in addition to replacement therapy with glucose. Oral propylene glycol or corn syrup are quick sources of energy and should be given at the rate of 200 ml four times daily along with 3-4 liters of concentrated oral rehydration fluid [23]. Ewe treated very early in the course of the disease generally responds favorably, but response to therapy is poor once ewe has become recumbent. So if the ewe is already comatose, treatment should focus on the rest of the flock [11].

Parenteral therapy

Therapy with glucose should be accompanied by the IV injection of isotonic sodium bicarbonate or lactated Ringer's solution and the administration of further fluids by a stomach tube. Treatment with recombinant bovine somatotrophin (0.15 mg/kg body weight) in conjunction with dextrose and electrolytes may result in a shorter duration of treatment, improves ewe survival and results in a greater viability of lambs born but reported results are not impressive [24].

Oral therapy

Propylene glycol or glycerin (110 gram per day) given by mouth is used to support parenteral glucose therapy. Success is reported with the oral drenching, every 4-8 hours, of 160 ml of a solution containing 45 g glucose, 8.5 g sodium chloride, 6.17 g glycine and electrolytes, which is available commercially as a concentrated oral rehydration solution. Reported recovery rates are 90% in early cases and 55% in advanced cases [23]. Treatment with insulin in addition to treatment with oral glucose precursors and electrolytes shows a significantly higher survival rate (87%) compared with treatment with oral glucose precursors and electrolytes alone [25].

Caesarean section

In advanced cases, a Caesarean section (C-section) may need to be performed to remove fetuses and save the ewe's life. Once animals become recumbent and refuse to get up, medical treatment is usually unrewarding

and a C-section is recommended to immediately remove the negative energy drain of fetuses from the mother [26]. It can be used as an alternative to replacement therapy. If ewes are in the early stages of the disease, removal of the lambs by C-section has the greatest success rate where the demand for glucose by the lambs is immediately removed and both the ewe and the lambs have a high chance of survival provided the C-section is conducted before there is irreversible brain damage in the ewe and the lambs are close to term. If the ewe is in the recumbent stage, then her chance of survival is low. C-section can still offer the chance of survival for lambs but also less viable at this stage and may be dead. Induction of parturition with prostaglandin $F_{2\alpha}$ is a further option but should only be used if the ewe is in the early stage of the disease as lambs will be delivered no earlier than 36 hours after therapy and often later. If the ewe is judged unlikely to survive this period, C-section is a better option [1].

Control and prevention

Control. When clinical cases occur, the rest of the flock should be examined daily for any evidence of ketosis and affected ewes should be treated immediately with propylene glycol or glycerol or oral glucose/glycine/ electrolyte solutions. Supplementary feeding of the flock should be commenced immediately with particular attention given to an increase in carbohydrate intake. Cereal grain starting at 0.5 Ib/head per day and increasing to 2 lb/head per day (0.25-1kg/head per day) for large frame breeds is recommended [27].

Prevention. Prevention of pregnancy toxemia involves three managemental goals. Adequate nutrition should be provided during the final weeks of pregnancy, there should be ample room for exercise and control of other conditions that might result in reduced feed intake or increase energy demand such as foot rot or parasitism [28]. Prevention can be readily achieved by nutritional means and is far more rewarding than therapy. Ewes must be fed in relation to their changing energy needs throughout the reproductive cycle [8]. Thus, ewes should not enter the last 6 weeks of gestation with a BCS less than 2.5. This can be prevented by good feeding management and ration formulation [11]. One major factor in the nutrition of the pregnant ewe is that of the unborn lamb. The gestation period in sheep is short as compared to many other animals and the fetal demand for nutrients and glucose is at its greatest during the last 2 months of pregnancy. In fact, about 70 % of the growth of the fetus occurs during the last 6 weeks of pregnancy; if twins are present, the increase in total weight is considerable. The total metabolic rate increases by at least 50 percent during late pregnancy. It has been shown that late pregnant ewes require about 50 % more feed if bearing a single lamb and about 75 % more feed if carrying twins. The increased amount of feed, however, sometimes exceeds the sheep's digestive capacity unless grain is substituted for part of the hay. Multiple fetuses will tend to crowd the animals digestive system and hence limiting intake, this is where concentrates can help. During the last 6 wk of gestation, grain is required as a source of carbohydrates in the ration to maintain the health of multiple-bearing ewes. Amount varies depending on forage quality, adult body weight, condition score and number of fetuses [11].

Maiden ewes should feed as a separate group in order to provide the requirement for growth in addition to the requirement for pregnancy. Attention should also be given to broken-mouthed ewes to ensure that they are maintaining an adequate body condition. Sudden changes in type of feed should be avoided and extra feed should be provided during bad weather. Shelter sheds should be available and in purely pastoral areas, lambing should not be planned before the pasture is well grown. A high incidence is often encountered in small, well-fed flocks where the ewes get insufficient exercise. In such circumstances the ewes should be walked 30 minutes daily and, if pasture is available, only concentrate should be fed so that they will be encouraged to forage for themselves [1].

CONCLUSION AND RECOMENDATION

The principal cause of pregnancy toxemia is low blood sugar (glucose) in relation with high energy demand of the fetus especially occurs in pregnant ewes carrying twins. Onset of the disease is often triggered by one of several types of stress including nutritional or inclement weather. The disease is most prevalent in ewes carrying two or more lambs. The disease also affects ewes that are extremely fat or excessively thin. Diagnosis of the disease is based on clinical sign, history, and clinical tests of low glucose, high ketones, and necropsy findings. Successful treatment of pregnancy toxemia requires early detection and quick replacement therapy with glucose. Therefore; it can be recommended to feed high energy concentrates and grains during the last month of pregnancy and follow proper management to minimize and avoid farm losses.

DECLARATIONS

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Authors' Contributions

A. Kelay participated in the planning, collecting the required articles for review and execution of the review as a leader. A. Assefa participated in the critically revision of the manuscript for important intellectual contents and all authors of this review paper have read and approved the final version submitted.

Competing interests

The authors declare that they have no competing interests.

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