Treatment and Control of Peri-Parturient Metabolic Diseases: Pregnancy Toxemia, Hypocalcemia, Hypomagnesemia

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KEYWORDS

• Goat • Hypocalcemia • Hypomagnesemia
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In general, peri-parturient metabolic diseases in ewes and does—pregnancy toxemia, hypocalcemia, and hypomagnesemia—are caused by the failure of animals to have their nutritional requirements met during late pregnancy and/or early lactation. These disorders can be significant causes of peri-parturient mortality of ewes and does.[1–3] Decreased intake of the respective nutrients, usually in association with increased requirements of the animals, contributes to development of the pathologic conditions. Various factors can predispose the animals to these diseases. The early stages of the pathologic conditions are characterized by reduced appetite, which leads to further reduction of the intake of nutrients, in turn precipitating development of the disease and increasing morbidity. This article provides guidelines on the treatment and control of 3 peri-parturient diseases in ewes and does, namely pregnancy toxemia, hypocalcemia, and hypomagnesemia.

PREGNANCY TOXEMIA

Pregnancy toxemia ("twin-lamb disease") is a metabolic disorder of pregnant small ruminants, caused by an abnormal metabolism of carbohydrates and fats, which

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occurs at the final stage of pregnancy. The disease occurs more frequently in ewes than in does; lean (body condition score <2 in the 5-point scale) or obese (body condition score ≥4) animals, as well as animals carrying 2 or more fetuses, are at higher risk of developing the disease. The disease is characterized by development of hypoglycemic encephalopathy. Animals show anorexia, depression, neurologic signs, and blindness, followed by recumbency and coma.[4] The salient paraclinical findings are hypoglycemia and hyperketonemia/hyperketonuria of affected animals.

Treatment of Clinically Ill Female Animals

Treatment of the disorder should be based on 2 general principles: (a) administration of energy sources and (b) removal of factors that increase energy requirements of affected animals. The efficacy of the treatment depends on early instigation which, in turn, relies on timely and correct diagnosis of the disease. However, even in cases of early instigation of treatment, this may still fail. In animals with signs of the terminal stage of the disease (neurologic signs, blindness, recumbency), treatment often leads to transient improvement of the general condition of the animal, which could subsequently deteriorate, with eventual death of the animal. In such cases, for welfare reasons euthanasia of affected animals would be recommended, even before instigation of treatment. Substandard welfare of sick animals adds to the financial constraints of treatment, which can be expensive but frequently fruitless. In fact, Sargison[5] has reported that, despite a full course of treatment of toxemic ewes, only one-third of the animals would likely survive.

In hospitalized animals, intensive care involves indwelling intravenous catheterization, followed by administration of glucose (5–7 g) every 3 to 4 hours until full recovery.[1]

In veterinary practice situations, emergency pharmaceutical treatment consists of oral administration of propylene glycol (600 mg/mL). Rook[1] recommended administration of 100 to 200 mL twice daily, whereas other investigators recommend 60 mL twice daily,[6,7] which is considered less likely to cause side effects. A better approach would be to start treatment with 2 doses, each 150 to 200 mL, on the first day, thereafter reducing it to 60 mL per dose. The regime should be followed for up to 6 days, depending on the improvement of the animal's condition. Alternatively, glycerol (60 mL/animal, twice daily for 3–6 days) may be administered. Sodium propionate, liquid molasses, sodium lactate, or ammonium lactate may also be used as glucose sources, but they are not metabolized as quickly as propylene glycol. High doses of all these substances can disrupt normal function of the animal's ruminal flora, thus predisposing to ruminal acidosis. Oral administration of a concentrated dextrose plus electrolytes solution at a dose of 160 mL/animal, 3 to 4 times daily for 3 to 6 days, has also been found to be effective.[8,9]

Administration of recombinant bovine somatotropin at 0.15 mg/kg body weight (BW)[7] or single administration of a slow-release formulation at 160 mg/kg BW[10] has been shown to be of some benefit. Administration of insulin (intramuscular administration of protamine zinc insulin, 20–40 IU/animal daily, every 2 days until recovery) restores glucose uptake and has been suggested as an adjunct to the energy treatments described here, to increase recovery rates of seriously ill ewes[1,11]; in financial terms, however, its use would be justified only in animals of high reproductive value. Flunixin meglumine (intramuscular administration at 2.5 mg/kg BW for up to 3 days) can also be of help as an adjunct therapy to the aforementioned protocols.[12]

Administration of broad-spectrum anthelmintic(s) for effective treatment of gastrointestinal nematodes and liver trematode parasites should be considered. In such a case administration of levamisole is not recommended, as it has been associated with causing abortion in animals during late pregnancy.[13]

In ewes and does at early stage of the disease, it is possible to attempt induction of parturition for removal of fetus(es), in order to decrease energy requirements of the pregnant animal. Induction of parturition can be attempted in ewes after the 140th day and in does after the 143rd day of gestation without compromising fetal development. Various protocols have been proposed for induction of parturition in small ruminants. Of these, administration of 15 to 20 mg of dexamethasone (ewes/does), 10 mg of betamethasone (ewes), or 2.5 mg of flumethazone (ewes/does) is the most appropriate scheme, leading to parturition of ewes within 40 to 45 ($\pm$10–15) hours or of does within 48 to 72 h.[14,15] As often in toxemic ewes and does, endogenous concentration of corticosteroids may be increased[6,9]; simultaneous administration of 0.375 mg cloprostenol in ewes or 15 mg prostaglandin $F_{2\alpha}$ in does would increase the efficacy of the regime. Induction should be followed by intravenous administration of 20% dextrose solution (dose: 200–300 mL/animal) or 50% dextrose solution (dose: 80–120 mL/animal) twice daily until parturition is completed. Animals should be monitored at regular intervals, because the regime often leads to dystocia and retention of fetal membranes.

In ewes and does at advanced stage of the disease, removal of fetus(es) should be performed by cesarean section. In such cases, prognosis is generally poor; survival rate of operated female animals does not exceed 60% and can be even smaller if the fetus(es) had died in utero and was (were) autolyzed.[16,17] Therefore, euthanasia of affected pregnant ewes or does should always be considered before starting surgery. If surgery is decided on, then throughout the operation dextrose solution should be administered intravenously to the animal.

Immediately after induced parturition or after surgery, animals should be administered a broad-spectrum antibacterial agent (as injectable solution), a nonsteroid anti-inflammatory agent (eg, flunixin meglumine), and oxytocin (5 IU daily for 3 days) to facilitate expulsion of fetal membranes and to prevent metritis.[18,19] After removal of fetuses, the general condition of the animal usually is improved. Often, however, it may deteriorate again, especially if the fetus had died in utero In such a case, intravenous dextrose administration in combination with electrolytes must be continued until full recovery of the animal.

Care for Newborn Lambs or Kids Born from Sick Female Animals

Newborn lambs/kids from ewes/does with pregnancy toxemia require increased care. These animals usually have a suboptimal birth weight, are stressed, and may be premature. If their cardiac or respiratory function is weak, their body should be massaged to induce respiration. Doxapram hydrochloride (5–10 mg/animal) should be administered by intravenous or subcutaneous injection or by sublingual dropping.[20] If the dam cannot produce an adequate amount of colostrum, the newborns should be given colostrum from another female in the flock/herd or from the “colostrum bank” of the farm at a dose of 50 mL/kg BW, 4 times in the first 24 hours of life. Subsequently it should be evaluated whether the ewe or doe would be able to produce enough milk for feeding the newborns; if this is not considered to be possible, artificial feeding should be undertaken.

Care for Other Animals in the Affected Flock/Herd

Pregnancy toxemia should always be considered to be a flock/herd problem.[1,2] Therefore, appropriate measures must be taken for the clinically healthy animals. Risk factors, both at individual level (eg, age, poor teeth, lameness, or other disease) and flock/herd level (eg, feeder space, protection from inclement weather, poor quality forage, and so forth) should be evaluated at the time of attending any ill animals.

A metaphylactic treatment course to other ewes/does on the farm can be considered, based on the appraisal of the healthy flock/herd.

Initially, a broad-spectrum anthelminthic treatment course should be administered to all animals if a diagnosis of gastrointestinal parasitism can be supported (eg, quantitative fecal egg count). Ideally, pregnant animals should then be grouped, according to (a) their body condition score and (b) the stage of pregnancy. This grouping helps improve feeding appropriate to the needs of each group, and prevents wasteful feeding to animals bearing one fetus or to animals in early pregnancy.[9] However, if this is not possible then high-energy supplementary feed should be provided to all pregnant animals on the farm. For convenience, these feeds (eg, vegetable fat or molasses) can be given as a "top-dress" feeding, up to 50 g/animal daily, supplementary to concentrate feed and high-quality hay. In intensively managed dairy sheep, administration of a propionic salt (sodium or calcium), at a dose of 20 g/animal daily during the last month of pregnancy is also beneficial.

The situation in the flock/herd should be reevaluated every fortnight. Animals at risk of developing pregnancy toxemia can be identified for individual feeding, to prevent development of the disease; this can be achieved by measuring β-hydroxybutyrate concentration in the blood of pregnant ewes and does during the last month of pregnancy. If the number of fetuses carried has not been identified, the value of 0.8 mmol/L should be considered to distinguish animals at risk of developing the disorder. Otherwise, if the number of fetuses carried has been determined, β-hydroxybutyrate concentration should be measured in the blood of animals carrying multiple fetuses only; in this case, the cutoff value to be used for identifying animals at risk is 1.1 mmoL/L.[9,21] If financial or labor constraints preclude examination of all animals as described, then examination of 10% to 15% of animals will provide valuable information. If blood measurement is not feasible, semiquantitative measurement in urine by using dipsticks can be advocated, but results should be considered cautiously. Animals found to have increased concentration of β-hydroxybutyrate in blood (over the aforementioned thresholds) or urine should be separated from other animals and monitored closely. If early signs of the disease are observed, individual treatment should be instigated immediately.

PERI-PARTURIENT HYPOCALCEMIA

Hypocalcemia ("parturient paresis," "lambing sickness") is an acute or subacute pathologic condition, which occurs more often shortly before or after parturition. The salient features of the disorder include reduced serum concentrations of calcium, progressive paralysis of smooth and striated muscles, recumbency, and lack of conscience.[22] The incidence of the disease is associated with imbalanced nutrition and/or improper handling and housing. In older animals, the ability of absorption and mobilization of stored calcium is reduced; thus, these animals are more susceptible to the condition.[23] In contrast to "milk fever" in cows, which always occurs at calving, hypocalcemia in ewes and does can develop from several weeks before until the first 2 weeks after parturition when the fetal skeletons are mineralizing. Incidence of the disease is usually less than 5%, only occasionally rising up to 20%. On the other hand, in intensively managed dairy flocks/herds the disease is more frequent after lambing, coinciding with the time of peak milk production. Calcium concentration in ewes' milk is almost double that in cows' milk[24]; because there are individuals producing over 3 L of milk daily, there is a high and prolonged demand of calcium during the first stage of lactation.[25]

At early stages of the disease, animals become isolated from the flock/herd and have a temporary stiff gait, with muscle tremors; potentially, they can become

hyperesthetic. Soon afterwards, they become hyposensitive and weak, and remain recumbent. Depleted muscle contractions result in constipation and decreased rumen motility, leading to development of bloat.[26,27] As disease progresses depression can occur, usually ending in coma. Ears are typically cold, although rectal temperature usually remains within the normal range.[22,28]

Hypocalcemia may coexist with pregnancy toxemia. Differential diagnosis between the 2 diseases is difficult on a farm level, and can be accurately performed only by measuring concentrations of calcium and β-hydroxybutyrate in the blood of affected animals.

Uncomplicated hypocalcemia responds immediately (within 5 minutes) to intravenous administration of calcium; this can also be used to confirm the diagnosis.[29] Intravenous administration of 30 to 60 mL of 20% calcium borogluconate solution usually is sufficient. A combination product containing phosphorus, magnesium, and/or potassium with dextrose can also be used and may be preferred. Calcium solution should be heated to 35°C to 40°C before administration. Administration must be performed slowly over 5 to 7 minutes, while the clinician monitors the animal's heart rate and rhythm; administration should be stopped at once if there is evidence of arrhythmia. Subsequently, an additional dose of 60 mL of calcium borogluconate, without dextrose, can be administered subcutaneously to ensure a more prolonged absorption. During subcutaneous administration, and as calcium solutions are irritant, the quantity to be administered should be divided into 2 equal volumes and injected at 2 different sites of the body. In view of the potential dangers associated with intravenous administration of calcium solutions, preference of the subcutaneous route over the intravenous route has been advocated.[30] However, dangers are minimized if appropriate precautions are taken, while intravenous administration offers the advantage of immediate response by the animal.

Calcium administration can be repeated after 24 hours, especially in high-yielding dairy animals, to avoid relapse of the disease. In such a case, an amount of 50 mL is administered subcutaneously, divided into 2 equal volumes and injected at 2 different sites of the body. The total amount of 170 mL (60+60+50 mL) is the maximum recommended to be administered in a ewe or doe. If no response is evident, the diagnosis should be reevaluated.[31,32]

In cases of prepartum hypocalcemia complicated with pregnancy toxemia, it is preferable to avoid intravenous administration, as calcium solutions can be fatal in animals with impaired liver function.[30,33]

For grazing animals, attention to calcium content of feeds during diet formulation and avoidance of unnecessary stressors usually suffice to reduce the risk of animals developing the disease.[32,34,35] Cereal pastures and hays have very low levels of calcium, so supplementation is required. Stressors such as transportation can precipitate the disease. Special attention should be given to feedstuffs containing oxalates, which precipitate formation of nonabsorbent compounds with calcium. Among feedstuffs commonly provided to small ruminants, beet pulp (oxalate content in dry matter: 1%–2%), alfalfa leaves (oxalate content 0.1%–1%), sugar beet leaves (oxalate content 2%–5%), and sesame meal (oxalate content 0.1%–0.25%) are the ones with the highest content of oxalates.[36] Thus, their increased inclusion in compound feeds for pregnant or lactating ewes and does should be avoided. The source of calcium supply is important; in general, inorganic calcium is more digestible than calcium contained in feedstuffs.[37]

There are no detailed data concerning prevention of the disease in dairy ewes and does. Perhaps an effective preventive strategy against the disease can be built on knowledge from dairy cows, in which the disease has been studied thoroughly.[38] This

knowledge should include control of body condition,[39] regulation of calcium,[40] magnesium,[41] and phosphorus[42] content in the feed, monitoring of cation/anion balance in the feed,[43] and regular monitoring of calcium concentration in the animal's blood.[44]

HYPOMAGNESEMIA

Magnesium deficit, leading to hypomagnesemia, is primarily an issue in animals grazing young, rapidly growing pasture with reduced magnesium content, especially during the spring or autumn. The disease is rare in ewes and does raised under intensive conditions, as nutrition of these animals is based on feeding concentrates to support increased production. The etiology of the disorder is complex, with numerous interacting factors influencing magnesium content in the diet, as well as its availability and absorption.[45] Increased potassium (eg, from alfalfa hay or haylage) and/or reduced sodium content in the diet, coupled with increased milk yield are the main risk factors for the disease.[46–48] Adult ewes and does have a limited ability to mobilize magnesium body reserves; thus, they are dependent on daily intake to meet their requirements.[49] Clinical signs are caused by spontaneous activation of neurons in the central nervous system by the decreased magnesium concentrations in blood, leading to tetany.[50]

Recumbent animals with seizures require immediate treatment and should be considered as emergency cases; their condition may deteriorate and they can die within hours of development of the neurologic signs. Administration of magnesium and calcium salts, separately or as a combination solution, is the recommended treatment, as often there is concurrent hypocalcemia.[51] Intravenous administration of a solution containing 4% to 5% magnesium chloride and 20% calcium borogluconate (50 mL) is ideal, but combinations of 2 different products, according to commercial availability, can also be considered. Recovery is generally quick, but subsequent relapses are common; therefore, additional subcutaneous administration, 12 to 24 hours later, is advisable.[30] When clinical cases occur in a flock/herd, it is advisable to provide clinically healthy animals on the farm with magnesium oxide at a dose of 7 g/animal, given per os,[52] to avoid further clinical incidents in the farm.

Prevention is best accomplished by providing mineral supplements, rich in magnesium content, to the animals before lambing and the beginning of grazing in lush spring pastures. As most of these mineral supplements are not palatable, adequate feed consumption should be regularly monitored and ensured. Decreasing potassium intake by animals may prevent the inhibitory effect on magnesium absorption, but this is not practical or applicable in grazing animals.[50] Sodium deficiency has the same consequences as increased potassium intake and, thus, can be a significant risk factor for grazing animals. Lick blocks containing magnesium and sodium chloride can help prevent sodium deficiency and promote magnesium intake.[53]

SUMMARY

This article reviews treatment and control of pregnancy toxemia, hypocalcemia, and hypomagnesemia, the important peri-parturient diseases of small ruminants. Treatment of pregnancy toxemia benefits from early instigation, that is, on timely diagnosis, and is based on administration of energy sources to sick animals. Removal of fetuses, by induced parturition or cesarean section, should also be performed. Individual cases within a farm require close monitoring of other animals present, as well as measures to avoid development of further clinical cases. Treatment of hypocalcemia is based on administration of calcium solution. Finally, hypomagnesemic animals need urgent treatment with calcium and magnesium solutions.

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