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Metabolic Periparturient Diseases in Small Ruminants: An Update

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Abstract: Metabolic diseases are major diseases affecting animal welfare, health and production of small ruminants' flocks for dairy and meat purposes. In breeding females, they mainly occur from six to eight weeks before and after parturition, respectively. The pregnancy toxemia and lactational ketosis are manifestations of hyperketonemia, primarily due to energetic deficit. Hypocalcemia and hypomagnesemia are related to the metabolic availably of calcium and magnesium, respectively. This review aimed to identify and discuss the current and most relevant aspects related to individual and herd heath management of these interrelated metabolic diseases with impact in the sheep and goats' farm sustainability. These diseases are primarily due to nutritional deficit, but homeostatic and homeorhetic disruptions are responsible for clinical signs and forms. Currently, their clinical diagnosis and monitoring are mainly supported by biochemistry from animal fluids, and bromatological evaluation of the feed. Epidemiological studies, measuring risks factors, also contributes for their prevention. Nevertheless, research on specific biomarkers and composite indexes related to these diseases, in a context of herd health management and precision medicine, are new pathways driven to a suitable and efficient animal production.

Keywords: small ruminants; pregnancy toxemia; hypocalcemia; hypomagnesemia; production diseases; prevention medicine

1. Introduction

Small ruminants are normally fed *ad libitum* whatever the production system, and food intake, as well as in other species, must cover the energy and nutrient requirements for their maintenance and physiological condition, i.e., lactation, pregnancy, dry period [1]. When reared in extensive, semi-intensive or intensive production systems, an economic outcome is sought, dependent on their function and productive capacity, in terms of gestation, lactation and growth, in accordance with productive purpose (generally dairy, meat or mixed).

Physiological transition between lactations (pregnancy-lactation) is challenging, and the emergence of metabolic and nutritional diseases depends on their genetic potential, and on the nutritional management or availability of a diet balanced in water, energy, protein, mineral, and vitamin [2,3]. Essential nutrients include carbohydrates (sugars, starch and fiber), proteins (amino acids), lipids, macroelements (sodium, calcium, phosphorus, zinc, magnesium and potassium), microelements (iron, iodine, copper, cobalt, selenium, among others), and fat-soluble vitamins (A, D, E and K) and water-soluble vitamins (B complex and vitamin C) [4], which mainly serve as co-factors of metabolic pathways.

Animals with high productive capacity are subject to a high food demand (input) and the intensification of metabolism, with potential homeostatic imbalances, to achieve the amounts of protein and energy necessary to produce protein (creatopoietic activity) and milk (lactogenesis) among others (output). This intensification, which, by inducing functional and lesional changes in the body's tissues and organs, causes the so-called "production diseases"[2–4]. Nutrient requirements during late pregnancy (around last six weeks) and lactation (around first eight weeks)

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are distinct [5,6], and gut and physiological (oxidative status) adaptation of dams also occurs during the transient period [7,8], exercising additional pressure on metabolic disturbance [9].

This critical review aimed to address an update on the main interrelated diseases of energy metabolism, derivate from ketosis, as well as mineral metabolism, hypocalcemia and hypomagnesemia, resulting from deficiencies or imbalances in nutrition, and changes in the respective homeostatic metabolism in sheep and goats during the periparturient period. Major issues related to the veterinary and engineering improvement of efficient production in farms were highlighted.

2. Pregnancy Toxemia and Lactational Ketosis

In terms of energy metabolism, small ruminants develop diseases that involve hyperketonemia in response to energy deficit, originating metabolic complications related to adipose tissue mobilization and loss of maternal glucose homeostatic control. This disruption can lead to pregnancy toxemia (PT) normally in the last 2-6 weeks of gestation (80% of cases) [10–12] or lactational ketosis (LK) in high-dairy producing ewes [13] and does [3], mainly during the 1st month of lactation. PT and LK are expressions of ketosis more at antepartum or postpartum, respectively, and more or less associated with fatty liver. Since PT has been studied for a long time, LK has been addressed more recently in the last two decades, regarding the improvement of milk yield, mainly in does.

2.1. Epidemiology

The prevalence of PT varies according to regions and farms. Morbidity rates in herds of up to 60%, reaching a mortality rate up to approximately 80% for mother and fetuses, even if a cesarean section is performed has been reported [14–18]. We can consider indicative a PT prevalence of around 2% in flocks and 10% in multiple pregnancies. PT may arise regardless of the animal´s aptitude, or LK, but is most commonly associated with highly dairy productive animals and twinning gestations (a synonym for PT is "twinning disease") [19,20]. Multiparous (2nd or greater pregnancy) and oldest females with body condition scores ≤2 (thin status) or ≥4 (obesity; scale 0 to 5) are considered more susceptible [12,21–23]. Proliferous breeds, e.g., *Merino* sheep and *Boer* goats, are prone to develop PT. Relevant environmental risk factors are temperature range and ventilation, lack of exercise and stress [24].

Unfortunately, unlike what happens with cattle, for small ruminants, KL has been less studied regarding its incidence and risk factors.

2.2. Etiopathology

PT is triggered by a deficient energy intake coupled with increased energy demand to support exponential fetal growth. Fetuses' weight reach 60 to 80% of their live weight at birth during the last weeks of gestation, consuming 30 to 40% of glucose/day [12,25]. Females with twin or triplet pregnancies require at least 180 to 240% more energy, respectively, than females with singleton pregnancies [25]. PT, as well as LK, can be classified as primary, due to a decrease in energy intake for any reason, and secondary, if intercurrent with other diseases (e.g., acidosis, dehydration, hypocalcemia, parasitic infections, or chronic wasting diseases) causing a decrease in intake [26,27].

Under normal conditions, small ruminants consume approximately 5-6% of their live weight of dry matter (DM) per day [28]. From middle (about 1.33 kg DM/day) to late pregnancy due to the pressure exerted by the pregnant uterus on the rumen, the ingestion capacity progressively decreases until parturition (about 1.21 kg DM/day). This decrease in DM intake is also associated with the development dynamics of rumen papillae according to the type of feed (amylolytic / cellulolytic) provided. In this way, from the kidding or lambing time, there is an increase in the amount of food ingested, reaching peak intake at approximately 8 weeks, and approximately 2-3 weeks later than the peak of lactation. As a result, approximately 2 to 6 weeks of the antepartum period and in the following 8 weeks after parturition, there is, to a greater or lesser extent, an insufficient energy supply causing hypoglycemia (normal serum levels of 2.2 to 3.3 mmol/L) which is compensated through

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mobilization (triglyceride hydroxylation) of adipose tissue reserves by lipolysis mediated mainly by the hormone glucagon, resulting in a visible loss of body condition scores, and the so-called NEB (negative energy balance) is established. When energy input exceeds energy output, generally after the 2nd month, excess energy is metabolized by lipogenesis mediated by the hormone insulin in adipocyte accumulations, mainly subcutaneous. When there is a negative energy balance, circulating non-esterified fatty acids from lipolysis are transported to the mitochondria of the hepatocyte and are metabolized there into three types of ketones, beta-hydroxybutyrate (BHBA), acetoacetate and acetone (which are strong acids causing metabolic acidosis) [29].

From the combination of the acyl group of ketones with coenzyme A (limiting factor) acetyl coenzyme A arises, an energy source in various tissues (mitochondria of skeletal muscle, mammary gland, heart and kidneys [30–32]. Oxidation of acetyl coenzyme A also produces lactic acid. Hyperketonemia occurs when high levels of circulating non-esterified fatty acids (NEFA) are metabolized in the liver (See the hepatic oxidation theory by Allen et al. [33]. As ruminants have limitations in the export of lipoproteins into the bloodstream at membrane level [34], hyperketonemia is normally associated with a certain degree of hepatic lipidosis due to diffuse lipid accumulation in hepatocytes, i.e., hepatic steatosis or fatty liver. This lipidosis cause liver dysfunction [35], with a poor prognosis when it reaches 35% of the liver weight [36]. In PT, hepatic steatosis assumes a relevant manifestation with impact in the evolution of the disease.

Ketosis is also classified as type 1 and type 2, similar to type 1 / type 2 diabetes mellitus in humans, and also known as thin cow syndrome and fat cow syndrome in cattle, respectively [37]. Ketosis type 1 occurs when the demand for glucose exceeds the capacity for neoglucogenesis. This type of ketosis characterized by low plasmatic levels of glucose and insulin, and high concentration of ketone bodies and carnitine acyl transferase 1 enzyme. In ketosis type 2, a high hepatic supply of NEFA occur, but without maximal stimulation of ketogenesis and neoglucogenesis, i.e., NEFA are not transported to the hepatic mitochondria. Ketosis type 2 is characterized by hyperglycemia, hyperinsulinemia and insulin resistance of peripheral tissues [38]. This type of ketosis is most likely to develop fatty liver mainly associated with PT. However, the mechanisms of insulin resistance and insulin sensitivity of peripheral tissue still not well understand in ruminant's species.

2.3. Diagnosis and Biomarkers

In PT, the main clinical signs, which serve as diagnosis in life, are the reduction in physical activity levels with apathy and anorexia in late gestation, showing odontoprises, nervous symptoms (hypoglycemic encephalopathy) and blindness [21,39]. Progressively, and over a period of 3 to 7 days, affected animals present ataxia and sternal recumbency (mainly in pregnancy toxemia), progressing to coma and death [40]. This evolution is mainly due to the diffuse hepatic steatosis. Similar symptoms can occur in LK, with decrease in milk production (hypogalaxia), but the evolution of the disease if less abrupt and intense, unless if concomitant severe fatty liver occurs.

Biochemistry plays a crucial role on diagnosis and prognosis ketosis, with emphasis for PT. Several metabolites and enzymes can serve as biomarkers for both purposes (Table 1). Biochemistry can serve as biomarkers, but due to the great variation of values, additional research is needed to establish accurate indicators for early diagnosis and prognosis of different status of these diseases.

Regarding the metabolic profiles, the measurement of serum BHBA levels, with thresholds between 0.8 and 1.7 mmol/L for subclinical ketosis and clinical form between 2.5 and 3 mmol/L, has been accepted to confirm the diagnosis of both diseases in ewes and does, [16,21,41–45].

Although hypoglycemia is common in cases of PT, up to 40% of cases present normal serum levels of glucose and >20% having hyperglycemia due to cases of insulin resistance in peripheral tissues [39]. However, different proportions on ambulatory veterinary clinic have been reported [46,47]. The variation of serum glucose levels (hypo, normo and hyperglicemia) seem primarily related to the ketosis type I or II, i.e., involving mechanism of insulin resistance in peripheral tissues. It is necessary to highlight that insulin resistance / sensitivity in peripheral tissues is an evolutionary survival protection of fetuses (in uterus) and offspring (trough lactation) [48]. The problem arises when the dysregulation occurs.

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Additionally, normal range (normoglycemia) of serum glucose levels varies between 50 to 80 mg/dL in small ruminants [49]. Further confirmation cerebrospinal fluid glucose concentrations can be more accurate than blood glucose concentrations which can serve as a diagnostic value together with the measurement of BHBA.

NEFA serum concentration may also be increased above 0.4 mmol/L, due to hepatic lipidosis. Mean serum levels of 0.6 ± 0.1 and 1.0 ± 0.2 (mmol/L) were reported in ewes affect by subclinical and clinical PT, respectively [43]. In does presenting clinical PT, Serum NEFA reached a mean of 1.7 ± 0.7 mmol/L [50] Regarding the lipid metabolism, plasmatic levels of triglycerides and cholesterol show a similar profile to NEFA.

Fructosamine, an irreversible conjugation between glucose and amino group of protein, can serve as indicator of blood glucose levels during the last two weeks and its low levels can be used as PT (see Table 1) or non-survival (< 0.2 mmol/L) predictor [43]. Nonetheless, some care is necessary interpreting cases of normo or hyperglycemia. Fatty liver is causing diffuse hepatic damage impairing albumin synthetisis as well as increased production of liver enzymes, mainly aspartate transaminase, gamma glutamyl transferase and lactate dehydrogenase, indictors of hepatocyte damage. Increase in creatine kinase has been justified by low protein intake (similar to potassium), and skeletal and myocardial muscle damage (e.g., recumbency) during the evolution of the disease [47,51].

Table 1. Thresholds of metabolic and oxidative biomarkers for clinical (and subclinical) pregnancy toxemia in ewes [43].

Biomarker	Cutoff	Se (%)	Sp (%)
Glucose (mg/dL)	-	-	-
(subclinical)	< 40.3	63.6	83.3
Fructosamine (mmol/L)	< 0.6	89.3	72.2
(subclinical)	< 1.0	90.0	75.3
NEFA (mmol/L)	> 0.7	86.4	70.6
(subclinical)	> 0.4	70.0	90.0
Triglycerides (mg/dL)	> 29.9	73.9	64.7
(subclinical)	> 20.5	72.7	83.3
Cholesterol (mg/dL)	> 71.0	73.9	70.6
Albumin (g/dL)	< 2.7	73.9	64.7
AST (U/L)	> 123.8	82.6	62.5
GGT (U/L)	> 76.3	81.0	66.7
(subclinical)	> 47.7	66.7	75.0
LDH (U/L)	> 760.3	81.0	66.7
(subclinical)	> 645.4	60.0	64.6
CK (U/L)	> 222.2	76.2	64.7
Calcium (mg/dL)	< 7.1	68.2	64.7
Potassium (mEq/L)	< 3.6	66.6	58.8
MDA (nmol MDA/mL)	> 29.3	78.2	64.7
(subclinical)	> 21.9	77.8	61.2
SOD (U/g Hb)	< 287.3	78.3	64.7
CAT (U/g Hb)	< 97.9	65.2	64.7

Calcium is intrinsically connected mainly to tissue reaction, and its deficit (ionized form) reduce the production of endogenous glucose in hyperketonemic ewes [52]. Moreover, Souto et al. [46] observed a positive correlation between insulinemia and plasmatic levels of total calcium (r = 0.51) or its ionizable fraction (Ca^{++}) (r = 0.52) in goats. Hypoinsulinemia is reported in both ewe [53] and does [51] and probably related to the adverse effect of NEFA on β-pancreatic cells or cortisol regulation. In fact, negative correlations between insulinemia and NEFA (r= - 0.70) or cortisol ((r= - 0.52) were observed in goats [46]. These findings highlight the complex relationships between different metabolites that should be deeply elucidated.

 doi:10.20944/preprints202409.2196.v

Regarding the oxidative stress, both normal NEB and PT induce reactive oxygen species (ROS) during late pregnancy, such as malondialdehyde (MDA), through lipid peroxidation [54]. MDA, a highly reactive compound causing mutations and cell damage, is a useful general indicator of oxidative status and, as its plasmatic levels increase, it can also serve as a predictor of diagnosis and prognosis. Inversely, superoxide dismutase enzyme catalyze ROS to hydrogen peroxide and, catalase enzyme helps to regulate this peroxidation process [43].

Due to the ROS effect on myocardial muscle, higher plasmatic levels of troponin I, a specific marker of cardiac myocyte damage, was observed in survivors PT ewes (0.7 ± 0.4 ng/mL) or non-survivors PT ewes (1.0 ± 0.5 ng/mL) than in healthy ewes (0.3 ± 0.0 ng/mL; P <0.001) [53]. Also, in this study, higher plasmatic levels of creatine kinase myocardial band, another marker of cardiac injury, were observed in non-survivors PT ewes (196.9 ± 58.1 U/L) than in healthy does (50.8 ± 0.4 U/L; P< 0.05). A similar pattern of troponin I was observed by these researchers [51] in does: 0.4 ± 0.2 vs 0.06 ± 0.02 ng/mL (P <0.05) for clinical PT and healthy does, respectively.

Aspartate transaminase (AST), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT)

Several biomarkers (Table 2) for prognosis of the clinical form of PT were identified by estimating mean differences according to recovery or death of clinically affected females. These biomarkers are still based on plasma metabolites, hormones or enzymes (biochemical and hormonal profiles) sampled in animals during the course of PT.

Table 2. Prognosis indicators (mean ± SE) of clinical pregnancy toxemia (PT) in ewes [43,55].

Biomarker	Survivors	Non-survivors
3-hydroxy-butyrate (mmol/L)	3.5 ± 2.6	4.3 ± 3.6
Fructosamine (mmol/L)	0.69 ± 0.09	0.32 ± 0.71
Creatinine (mg/dL)	1.46 ± 0.23	3.13 ± 0.31
LDH (U/L)	678.4 ± 56.7	988.5 ± 66.9
Cortisol (mmol/L)	52 ± 80	72 ± 98
Insulin (pmol/L)	66 ± 42	37 ± 12
Potassium (mEq/L)	4.4 ± 1.0	4.1 ± 1.0
MDA (nmol MDA/mL)	25.5 ± 4.0	41.0 ± 3.2
Troponin I (ng/mL)	0.7 ± 0.4	1.0 ± 0.5

Lactate dehydrogenase (LDH), malondialdehyde (MDA).

The determination of thresholds and their accuracy are needed to effectively apply them during clinical approach. Also, further research of composite indexes regarding the interrelationship between biomarkers, as reported previously for energy metabolism, in both diagnosis and prognosis indicators can provide more accurate tools to approach this problem in farms.

2.4. Treatment and Prevention

The implementation of treatment in animals that present the clinical form of PT is urgent, and even at an early stage (before decubitus) it may not be effective, or at any stage there may be a transient clinical improvement followed by deterioration, eventually culminating in the death of the animal. Euthanasia may be indicated in these cases of deterioration since even if treated, 2/3 of affected animals have a poor prognosis (death) [21,56]. Therefore, a cesarean section to abruptly interrupt the flow of glucose to the fetuses, or birth induction from 140 and 143 days of gestation in sheep and goats, respectively, so as not to compromise fetal development, can be considered. Nonetheless, perinatal mortality is common. Indeed, fetuses typically have low birth weight, suffering from fetal stress and an association between hyperglycemia and fetal death has been suggested [17].

The medical treatment of both diseases is based on the immediate supply of isotonic glucose solutions (5-7 g at 5%), which should be administered parenterally (intravenously), ideally (for example in hospital situations) every 3-4 hours until recovery [18]. However, in field conditions this

 doi:10.20944/preprints202409.2196.v

dosage is not practical, supplementation with oral drenching of glucogenic precursors (propylene glycol, lactate or sodium propionate, among others) is essential and with similar effectiveness of IV infusions [57]. Propylene glycol, administered orally twice a day, in an initial dose of 150-200 ml followed by 60 ml for up to six days [14,21], is the precursor of choice.

The animal's rehydration can be maintained by oral administration of electrolytes (associated or not with dextrose) 3 to 4 times a day. The insulin-zinc-protamine complex, administered subcutaneously at a dose of 20–40 IU every 2 days until the animal recovers, has shown good efficacy in the treatment of these conditions in sheep [55]. More recently, metabolic prognostic indicators have been studied, showing that high blood urea nitrogen levels or serum bicarbonate concentrations < 15 mEq/L (in goats) are associated with poor prognoses [58].

The prevention of hyperketonemia is based, in the first instance, on the effective supply of a balanced diet in nutrients and energy density so that, in the critical periods of occurrence, there is adequate functioning of the rumen and its flora and consequently the maximization supply of metabolizable energy. The nutritional management of animals depends on their productive capacity. In animals with low milk production, ruminal pH is normally above 6, which reduces the probability of encountering chronic ruminal acidosis in these herds, normally grazing, with a low concentrate/fiber feed ratio. However, when it becomes necessary to increase the energy density of the diet (up to a ratio of 1.5), rumen pH tends to drop to values below 5.8 for more than 6 to 8 hours a day, causing sub-acute ruminal acidosis [59,60]. The chemical action of low pH, in addition to being able to cause ruminitis, alters the local flora with imbalances in the production of volatile fatty acids (decrease in propionic acid) [59] with the formation of toxic amino acids such as histidine. An optimal body condition score should be reached before the susceptible period in order to avoid weak and obese females at this time [61].

Despite the semiquantitative determination of some metabolites in milk (e.g., BHB), the sample analysis is performed off-site at laboratory, even some on-farm handheld devices have been studied, such as BHB meter for ketotic ewes [62] and does [42,63]. New sensors and algorithms are continuously under research (e.g., Brobst et al. [64], for glucose in does) and seems to be the complement of the decision tree given by the mentioned threshold and composite indexes for effective implementation of the precision medicine. Another approach for herd health management of metabolic diseases is based on combination of sensor data and health monitoring, such as described in dairy cows by Sturm et al. [65]; but this approach remains incipient and more applied development is required.

3. Hypocalcemia

When discussing disorders of mineral metabolism, hypocalcemia and hypomagnesemia appear as the dominant ones in ruminants. These disturbances in mineral metabolism are associated with the greater demand for productivity and individual efficiency, but also observed in extensive production systems.

Subclinical and clinical hypocalcemia can be considered dependent of the progressive plasma calcium levels, like hyperketonemia, but the thresholds to differentiate them are not accurately determined. Due to the disturbance of soft muscle contraction, hypocalcemia is a risk factor for other postpartum diseases and delayed uterine involution. Moreover, it was recently suggested that subclinical hypocalcemia can reduce lamb survival, mainly during the first week [66].

3.1. Epidemiology

Hypocalcemia occurs at specific periods, such as peripartum, due to the demand for calcium by fetuses or milk production, during which serum and interstitial replacement is insufficient [67]. Normal serum calcium (Ca) levels range from around 2.2 to 2.9 mmol/L (8.9 - 11.7 mg/dL), 2.8–3.2 mmol/L for sheep and 2.2–3.05 mmol/L for goats) [49,68]. Its diffusing ionizable fraction (Ca^{++}) represent about half of total calcium in serum. The serum levels of Ca^{++} are affected by the acid-base balance to diffuse into different tissues where it is essential to promote muscle contraction, among numerous other functions. In does, similar to cows and in contrast to ewes, hypocalcemia appears

 doi:10.20944/preprints202409.2196.v

mainly after parturition (up to 8 weeks). The fetoplacental mass is larger and the udder is smaller in pregnant ewes than cows, mainly in multiple pregnancies [69]. Hypocalcemia is more likely to occur in does with high production level or multiple fetuses, in which calcium concentration in milk is approximately 32.5 mmol/L (130 mg/dL) [68,70]. However, similar to ewes, hypocalcemia can also appear in does during the *ante-partum* from approximately 80 days of gestation, with greater demand for calcium due to fetal skeleton mineralization (1-3 weeks) and later to colostrum [71], during the first week [72].

The clinical incidence of hypocalcemia is generally less than 5%, however, severe outbreaks may involve up to 30% of the flock. Mortality can reach 90% of untreated animals [72]. Older animals (4-6 years) are considered more susceptible due to their lower capacity to regulate intestinal absorption and bone mobilization of calcium [73,74]. Other relevant risk factors that, associated with the most susceptible periods precipitate the occurrence of the disease are reported in Table 3.

Table 3. Risk factor of hypocalcemia in ewes and does [73,75].

Age
Females with multiple fetuses
Heavy lactation
Animal transportation
Poor-quality grassy or cereal hays and pastures (low levels of calcium)
Forages with high levels of potassium and/or low levels of sodium and magnesium
Corn silage (low levels of calcium)
Grain cereals (low levels of calcium and sodium)
Feed containing chelators, such as oxaloacetate from beet pulp and leaves (*Beta vulgaris*), and alfalfa leaves (*Medicago sativa*)
Vitamin D deficiency which depresses gastrointestinal calcium absorption (housed animals during winter)
Improper Ca and P ratio (2:1), e.g., from cereal grains
Stress (e.g., intense handing, weather changes)

3.2. Etiopathology

The thresholds to define hypocalcemia are 2 mmol/L and 1.1 mmol/L of total serum calcium and Ca^{++}, respectively [75].

Abrupt change in feed or fasting (e.g., transportation) can origin an outbreak.

Calcium homeostasis is regulated by parathormone (parathyroid hormone), which increases serum levels, and calcitonin, which lowers them, with calcitriol (1,25-dihydroxycholecalciferol, the active form of vitamin D) playing an important role in intestinal absorption and bone mobilization of calcium without increasing renal excretion [76,77]. Also, magnesium plays a relevant role to support adequate production of parathormone, especially in presence of moderate hypocalcemia [78].

3.3. Diagnosis and Biomarkers

Hypocalcemia is characterized by acute or subacute-onsets, and rapid development of clinical signs (e.g., ataxia, progressing to depression, recumbency, comatose and death) related to muscle flaccidity due to the progressive paralysis of smooth and striated muscles. Hyperesthesia and tetany can be observed in does rather than flaccid paralysis [69]. Hypocalcemia, in small ruminants (like in cows), increases the susceptibility of presenting dystocia and retained placenta, due to a reduction of muscle contraction and retardation of uterine involution [73].

Definitive diagnosis can only be made by assessment of calcium concentration in blood (<2 mmol/L).

3.4. Treatment and Prevention

 doi:10.20944/preprints202409.2196.v

Treatment of affected animals must be immediate, carried out with slow intravenous administration (5-7 minutes) of calcium salts heated to 35-40ºC (30 to 60 mL of 20% calcium borogluconate solution). Calcium-containing products also containing additional glucose, phosphorus, magnesium and or potassium have additional therapeutic value. Concomitant cardiac monitoring is necessary to prevent arrhythmias. The subcutaneous administration of 50-60 mL of 20% calcium borogluconate, divided into 2 or 3 equal quantities and administered to different parts of the body, as calcium solutions are irritating and allows a slower absorption. Calcium administration can be repeated after 24 hours, preventing relapses [21].

Prevention involves controlling risk factors and meet the nutrient requirements for small ruminants (National Research Council, 2007) in periparturient ewe and dairy does, increase the calcium: phosphorus ratio (>1.5:1), meet vitamin D and total calcium requirements (calcium carbonate is the common supplemental source) [79]. Although some of the protocols adapted from dairy cattle can be used (possible limitation of calcium intake before critical periods, and anionic diets), it is necessary to consider the specificities of the occurrence of this disease in small ruminants. Does adapt efficiently to acidogenic diets which cause transient metabolic acidosis by increasing intestinal absorption and bone mobilization of calcium, even if serum levels remain constant [80,81]. Monitoring calcemia in groups of animals considered at risk or preceding periods of higher expected incidence are relevant indicators for the control and prevention of the disease.

4. Hypomagnesemia

Some synonyms of hypomagnesemia are hypomagnesaemic tetany, grass staggers, wheat pasture poisoning, milk or lactation tetany, denoting its symptoms or occurrence.

4.1. Epidemiology

Older animals reared under grazing system are the most affected. Hypomagnesemia is associated with pastures where young growing plants prevail (spring grain forage), with lower levels of magnesium or sodium, or when grass fertilization with high levels of potassium is applied [82]. However, this condition can also occur in fast-growing lambs or kids fed with replacement milk. A simple magnesium deficiency in diet, or any disorder causing a reduced availability and absorption in magnesium may lead to this unbalance.

4.2. Etiopathology

For instance, at ruminal level, due to conversion to an insoluble form or excessive calcium and potassium in the diet (input), or even in animals with high milk yield, mainly during early lactation (output; productive losses), can lead to hypomagnesemia. It is characterized by low blood serum magnesium concentrations (<0.6 mmol/L; <1.1 mg/dL), which induce changes in neuromuscular transmission. Magnesium homeostasis is not modulated by any hormonal system [72,83].

Ionized magnesium (Mg^{2+}) is mainly absorbed through rumen epithelial cell by two uptake mechanisms (potential-dependent and potential-independent). Other ionized molecules, such as high concentrations of $NH4^{+}$ and K^{+} or increase of ruminal pH can decrease the absorption magnesium, contrarily to high concentrations of short-chain fatty acid produced by ruminal microbiota [84].

4.3. Diagnosis and Biomarkers

Predominant nervous clinical signs persist resulting in episodes of tetanic contractions and convulsions, consequently in muscle excitability, incoordination and finally paralysis. The disease quickly progresses to recumbency and paddling, with immediate diagnosis and treatment required, to avoid death within a few hours [85].

Serum or plasma magnesium can be measured to diagnosis hypomagnesemia as previously mentioned. Nonetheless, even the threshold of 0.6 mmol/L is considered, the blood magnesium

 doi:10.20944/preprints202409.2196.v

concentration can increase after an episode of tetanic contractions. In this situation, the measurement of magnesium concentration from cerebrospinal fluid can done a more accurate interpretation.

4.4. Treatment and Prevention

Intravenous administration of 50 mL of 5% magnesium chloride, associated or not with 20% calcium borogluconate in the same dose, is recommended and animals usually respond quickly, although short-lived. Likewise, as in hypocalcemia, it is also recommended to administer a similar dose (every 12 to 24 hours) subcutaneously or in oral supplements to avoid relapses [86].

Its prevention is mainly associated with supplementation of magnesium salts (which are poorly palatable) up to 0.6% of dry matter during periods of greatest risk, namely from late pregnancy through early lactation [83,87]. Supplementation of 7 g of magnesium oxide (MgO) per animal/day is recommended in herds where this problem occurs. However, the *ad libitum* availability of mineral blocks containing magnesium and sodium must be ensured in herds, in general.

5. Conclusions

Metabolic diseases of periparturient ewes and does are one of the most relevant problems in farms. Manifestations of the energetic or nutrient deficit and metabolic disruption, lead to different forms of ketosis (hyperketonemia) in small ruminants which is also interrelated with hypocalcemia and hypomagnesemia. PT is the most prevalent form of ketosis, intrinsically related to fatty liver, with high relevance in ewes carrying multiple pregnancy. Several biomarkers have been studied and applied in field conditions. Nonetheless, the large broad of factors influencing the surge and course of ketosis, someone poor elucidated (e.g., pathophysiological mechanisms, insulin resistance, oxidative stress) cause limitation to their effective use and misinterpretation of the results in some circumstances. A holistic approach, regarding all the occurrence of all these metabolic issues (ketosis, hypocalcemia, hypomagnesemia) to better define the biomarkers and their cutoffs, or their combined indexes is required to diagnose, treat, control and prevent these occurrences in farms. Must probably, the feasible combination of sensors and algorithms, at engineering level, will be the next disruptive step regarding medicine precision. The health monitoring integrating information from different sources (animal health, risk factors, environment, nutrition and feed analysis) converging in a real-time central database can allows prediction and decisions to improve the efficiency of animal health, welfare and production during the periparturient period.

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