

Review

Metabolic Periparturient Diseases in Small Ruminants: An Update

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

Keywords: sheep; goats; pregnancy toxemia; hypocalcemia; hypomagnesemia; production diseases; preventive medicine



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1. Introduction

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

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

Animals with high productive capacity are subject to a high food demand (input) and metabolism intensification. Potential homeostatic imbalances can occur to achieve the amounts of protein and energy necessary to produce a protein (creatopoietic activity) and milk (lactogenesis), among others (output). This metabolism intensification, which, by

inducing functional and lesional changes in body tissues and organs, causes the so-called “production diseases” [2–4]. Nutrient requirements during late pregnancy (around the last six weeks) and lactation (around the first eight weeks) are distinct [5,6]. Dams’ gut and physiological (oxidative status) adaptation also occurs during the transient period [7,8], exercising additional pressure on metabolic disturbance [9,10].

This critical review mainly aimed to address an update on the main interrelated diseases of energy (ketosis) and mineral (hypocalcemia, hypomagnesemia) occurring during the periparturient period of sheep and goats. Major issues related to the veterinary and engineering improvement of efficient production in farms were highlighted. Diagnosis, treatment, and prevention at individual and herd levels are discussed with emphasis on diagnostic and prognostic biomarkers.

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. As a consequence, pregnancy toxemia (PT) normally occurs in the last 2–6 weeks of pregnancy (80% of cases) [11–13]. After parturition, lactational ketosis (LK) can develop in high-dairy-producing does [3] and ewes [11], 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 [10]. Since PT has been studied for a long time, LK has been addressed more recently in the last two decades due to the genetic improvement in milk yield, mainly in high-producing dairy does.

2.1. Epidemiology

PT prevalence varies according to regions and farms. Morbidity rates in herds of up to 60%, reaching a mortality rate of up to approximately 80% for mothers and fetuses, even if a cesarean section is performed, have been reported [14–20]. PT prevalence of around 2% in flocks and 10% in multiple pregnancies is considered indicative. PT, as well as LK, may arise regardless of the animal’s productive purpose. They are most commonly associated with highly dairy-productive animals (LK) and twinning gestations (a synonym for PT is “twinning disease”) [21,22]. 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 [13,23–25]. 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 [23].

Unfortunately, unlike what happens with cattle, for small ruminants, LK 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 reaches 60 to 80% of their live weight at birth during the last weeks of gestation, consuming 30 to 40% of glucose/day [13,26]. Females with twin or triplet pregnancies require at least 180 to 240% more energy, respectively, than females with singleton pregnancies [26]. PT, as well as LK, can be classified as primary and secondary. Primary ketosis is due to the energy deficit itself. Secondary ketosis develops intercurrently with other diseases (e.g., acidosis, dehydration, hypocalcemia, parasitic infections, or chronic wasting diseases), causing a decrease in feed intake [27,28]. Following severe undernutrition is normal, and a homeorhetic adaptation occurs [29]. The problem arises when the disruption of this adaptative mechanism occurs.

Under normal conditions, small ruminants consume approximately 5–6% of their live weight of dry matter (DM) per day [30]. From middle (about 1.33 kg DM/day) to late pregnancy, and 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, and also regarding LK, there is an increase in the amount of feed ingested from the kidding or lambing time, reaching peak intake at approximately eight weeks in lactation. The peak intake occurs 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).

In ruminants, the energy deficit is compensated through mobilization (triglyceride hydroxylation) of adipose tissue reserves by lipolysis, which is mediated mainly by the hormone glucagon. A loss of body condition score is observed, and the so-called negative energy balance (NEB) is established. When energy input exceeds energy output, generally after the 2nd month of lactation, excess energy is metabolized by lipogenesis mediated by the insulin hormone, resulting in adipocyte accumulations, mainly subcutaneous. When NEB occurs, circulating non-esterified fatty acids (NEFA) originating from adipocyte 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) [31].

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 [32–34]. Oxidation of acetyl coenzyme A also produces lactic acid. Hyperketonemia occurs when high levels of circulating NEFA are metabolized in the liver (see the hepatic oxidation theory by Allen et al. [35]. As ruminants have limitations in the export of lipoproteins into the bloodstream at the membrane level [36], 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 causes liver dysfunction [37], with a poor prognosis when it reaches 35% of the liver weight [38]. In PT, hepatic steatosis assumes a relevant manifestation with an impact on 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 [39]. Ketosis type 1 occurs when the demand for glucose exceeds the capacity for neoglucogenesis. This type of ketosis is characterized by low plasmatic levels of glucose and insulin and high concentrations of ketone bodies and carnitine acyl transferase 1 enzyme. In ketosis type 2, a high hepatic supply of NEFA occurs, but without maximal stimulation of ketogenesis and neoglucogenesis, i.e., NEFA is not transported to the hepatic mitochondria. Ketosis type 2 is characterized by hyperglycemia, hyperinsulinemia, and insulin resistance (IR; i.e., reduced responsiveness to insulin by peripheral tissues) [40]. This type of ketosis is most likely to develop fatty liver, mainly associated with PT.

It is necessary to highlight that IR or insulin sensitivity in peripheral tissues is an evolutionary survival protection (i.e., normal homeorhetic adaptation) of fetuses (in the uterus) and offspring (through lactation) [3,41]. The problem arises when the dysregulation occurs. IR is closely related to oxidative stress [42] and metabolic inflammation [41] in animals with high BCS [43]. These last two reviews elucidate several aspects of this issue in ruminants. However, the mechanisms of IR and insulin sensitivity in peripheral tissues are still not well understood in ruminant species. This is a very complex subject. As an example of a practical outcome, the 25-hydroxy-VitaminD (25VitD) was recently suggested as a plasma biomarker to predict the occurrence of PT in ewes four weeks before lambing due to its influence on insulin secretion [44]. Nonetheless, the precise mechanisms of action need further elucidation to establish potential interactions between subclinical hypocalcemia and the degree of IR in ketosis type II.

2.3. Diagnosis and Biomarkers

In PT, the main clinical signs that serve as a 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 [24,45]. Progressively, and over a period of three to seven days, affected animals present ataxia and sternal recumbency (mainly in pregnancy toxemia), progressing to coma and death [46] (Figure 1). Dehydration and ketoacidosis develop concomitantly. This evolution is mainly due to the diffuse hepatic steatosis. The degree of fat infiltration in the liver can be achieved through histological evaluation at necropsy [27,45], or even in live animals by a liver biopsy.

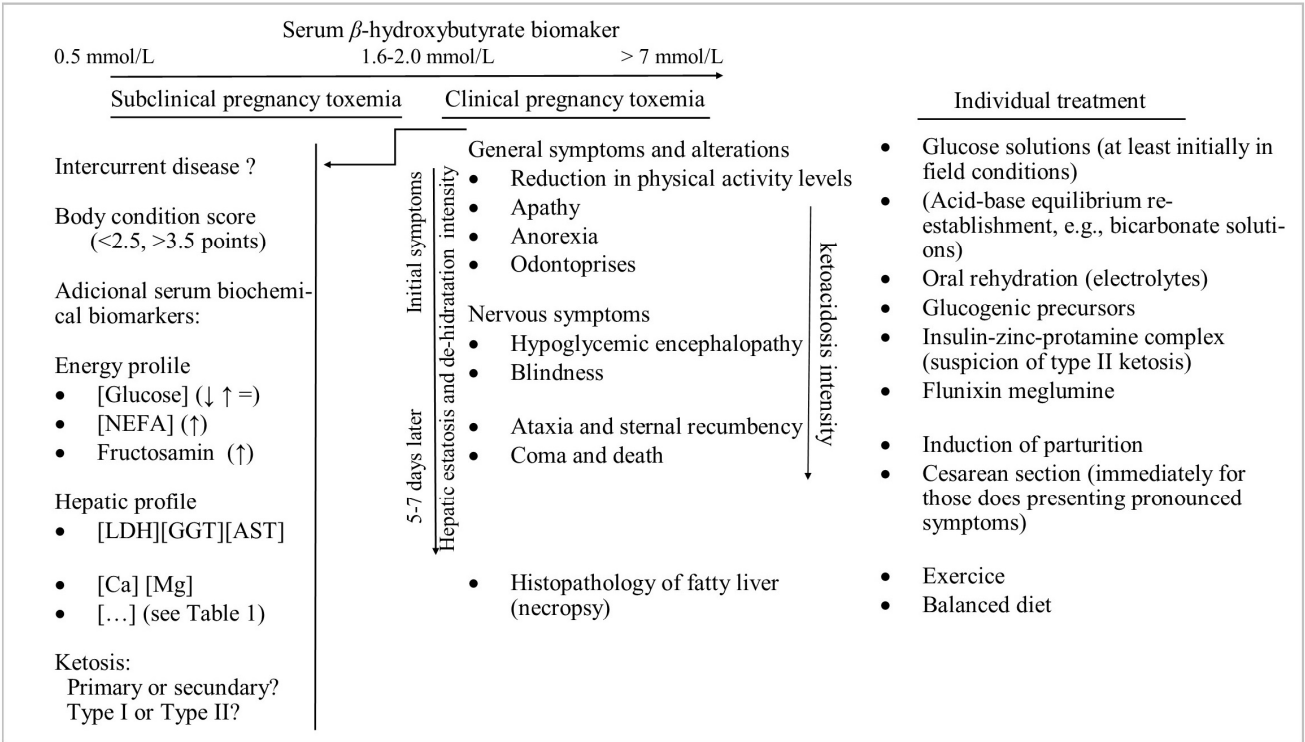


Figure 1. Diagram of diagnosis and therapeutic procedures of pregnancy toxemia in small ruminants. Non-esterified acids (NEFA), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), aspartate transaminase (AST), calcium (Ca), and magnesium (Mg).

Similar symptoms can occur in LK, with a decrease in milk production (hypogalaxia), but the evolution of the disease is less abrupt and intense unless concomitant severe fatty liver occurs.

Biochemistry plays a crucial role in the diagnosis and prognosis of ketosis, with emphasis on PT. Several metabolites and enzymes can serve as biomarkers for both purposes (Table 1).

Biochemical biomarkers are useful tools, but due to the great variation of values, additional research is needed to establish accurate indicators for early diagnosis and prognosis of different statuses 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 [19,24,47–51]. Nonetheless, the clinical approach of individuals requires the determination of more biomarkers to evaluate the status of different body organs and systems.

Although hypoglycemia is common in cases of PT, up to 40% of cases present normal serum levels of glucose, and >20% have hyperglycemia due to cases of insulin resistance in peripheral tissues [45]. However, different proportions of glycemia (hypo, normo, and

hyperglycemia) in the ambulatory veterinary clinic have been reported [52,53]. The normal range (normoglycemia) of serum glucose levels varies between 50 to 80 mg/dL in small ruminants [54]. The variation of serum glucose levels seems primarily related to ketosis type I or II, i.e., involving the mechanism of insulin resistance in peripheral tissues. Some composite indices, such as surrogate indices, have been applied to dairy cows [55] and goats [56] to estimate insulin sensitivity/resistance from glucose, NEFA, BHBA, and insulin. But like in human medicine (e.g., [57]), cut-offs are required to predict its occurrence and the level of intervention (e.g., the dose of insulin to be administered).

Table 1. Thresholds of metabolic and oxidative biomarkers for clinical (and subclinical) pregnancy toxemia in ewes [47].

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

Non-esterified acids (NEFA), 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).

Further confirmation of 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 affected by subclinical and clinical PT, respectively [47]. In does presenting clinical PT, Serum NEFA reached a mean of 1.7 ± 0.7 mmol/L [58]. Regarding the lipid metabolism, plasmatic levels of triglycerides and cholesterol show a similar profile to NEFA.

Fructosamine, an irreversible conjugation between the glucose and amino group of protein, can serve as an indicator of blood glucose levels during the last two weeks and as a consequence of timeline diagnosis of subclinical forms of ketosis. Its low levels can be used as PT (see Table 1) or non-survival (<0.2 mmol/L) predictor [47]. Nonetheless, some care is necessary in interpreting cases of normo or hyperglycemia. Fatty liver is causing

diffuse hepatic damage impairing albumin synthesis as well as increased production of liver enzymes, mainly aspartate transaminase, gamma-glutamyl transferase, and lactate dehydrogenase, indicators of hepatocyte damage. The 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 [53,59].

Calcium is intrinsically connected mainly to tissue reaction [60], and its deficit (ionized) form reduces the production of endogenous glucose in hyperketonemic ewes [61]. Moreover, Souto et al. [52] 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 [62] and does [59] and is 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 [52]. These findings highlight the complex relationships between different metabolites that should be deeply elucidated, including with IR, such as previously mentioned.

Regarding oxidative stress, both normal NEB and PT induce reactive oxygen species (ROS) during late pregnancy, such as malondialdehyde (MDA), through lipid peroxidation [63]. 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, the superoxide dismutase enzyme catalyzes ROS to hydrogen peroxide, and the catalase enzyme helps to regulate this peroxidation process [47].

Due to the ROS effect on myocardial muscle, higher plasmatic levels of troponin I, a specific marker of cardiac myocyte damage, were 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; $p < 0.001$) [62]. 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 [59] in does: 0.4 ± 0.2 vs. 0.06 ± 0.02 ng/mL ($p < 0.05$) for clinical PT and healthy does, respectively.

Several other serum or plasma diagnostic biomarkers were reported in the literature, mainly in case-control studies, as summarized in Table 2. However, the effective usefulness of each one in veterinary practice should be evaluated according to the different forms of diseases. This is relevant to establishing specific protocols for different biomarker profiles, including training artificial intelligence models.

Table 2. Additional blood diagnostic and prognostic biomarkers to evaluate tissue and fluid alterations regarding pregnancy toxemia [64–68].

Biomarker	Clinical Value
Total proteinemia and globulins	Liver dysfunction
Urea and blood urea nitrogen	Renal dysfunction
Glycosylated hemoglobin	Persistent hypoglycemia
Acute phase proteins	
Amyloid A and haptoglobin	Liver dysfunction
Glycoprotein α -1 acid	Lipid metabolism disfunction
Glutathione peroxidase (GSH-Px) enzyme	Oxidative stress
Acetylcholinesterase	Liver dysfunction
Paraoxonase enzyme	Inflammation and oxidative stress
Pro-inflammatory cytokines:	
Tumor necrosis factor-alpha ($\text{TNF}\alpha$)	
Interleukin-6 (IL-6)	Metabolic inflammation
Interleukin-1 β (IL-1 β)	
Interferon-gamma (IFN- γ)	

Several biomarkers (Table 3) for prognosis of the clinical form of PT in ewes 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. In goats, Lima et al. [45] observed a mortality of 100% when blood pH reached 7.15 or less. Other additional potential prognostic biomarkers for this last species are reported in Table 4.

Table 3. Prognosis indicators (mean $\pm$ SE) of clinical pregnancy toxemia (PT) in ewes [47,69].

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

Lactate dehydrogenase (LDH), malondialdehyde (MDA).

Table 4. Prognosis indicators (median and range) of clinical pregnancy toxemia (PT) in goats [45].

Biomarker	Survivors	Non-Survivors
K ⁺ (mmol/L)	3.7 (3.5–4.3)	2.7 (1.8–3.8)
pH	7.39 (7.30–7.43)	7.13 (6.84–7.45)
HCO ₃ [−] (mmol/L)	21.0 (14–35)	8.3 (3.3–21)
pCO ₂ (mmHg)	33 (28–56)	26 (16–42)

Ionized potassium (K⁺); bicarbonate (HCO₃[−]); partial pressure of carbon dioxide (pCO₂).

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 [70].

The determination of thresholds and their accuracy are needed to effectively apply them during the clinical approach. Also, further research of composite indices 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. It should also be highlighted that prognosis biomarkers have an impact on the tree's decision on the most appropriate treatment regarding dams and even offspring survival [18,71].

2.4. Treatment

Treatment implementation in animals that present the clinical form of PT is urgent, and even at an early stage (before decubitus), it may not be effective. 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) [24,72]. Therefore, a cesarean section can be considered 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. Nonetheless, perinatal mortality is common. Indeed, fetuses typically have low birth weight and suffer from fetal stress, and an association

between hyperglycemia and fetal death has been suggested [18]. According to Lima et al. [12] blood pH can serve as an indicator to interrupt pregnancy and improve the likelihood of does and offspring survival. An immediate cesarian section should be done at $\text{pH} < 7.12$. Parturition can be induced by dexamethasone and/or synthetic analogs of prostaglandin F₂-alpha for pH between 7.12 and 7.20, avoiding the cesarian section [45]. Note that the normal blood pH ranges between 7.31 and 7.45 [12], and only medical treatment and nutritional management are needed for mild symptoms.

Medical treatment of both diseases is based on the immediate supply of isotonic (5–7 g at 5%) or hypertonic (50 mL at 10–50% [73]) glucose solutions, which should be administered parenterally (intravenously), ideally (for example in hospital situations) every 3–4 h until recovery [14]. However, in field conditions, this dosage is not practical. Some research is done with the intent to supplement glucose per os (e.g., inducing the reticular groove closure) but remains experimental [74]. The supplementation with oral drenching of glucogenic precursors (propylene glycol, glycerol, lactate, or sodium propionate, among others) is essential to provide a source of glucose and has similar effectiveness to IV infusions [75,76]. Propylene glycol, administered orally twice a day in an initial dose of 150–200 mL followed by 60 mL for up to six days [20,24], is the precursor of choice. However, glycerol can promptly exchange the blood concentration of glucose due to its advanced entry point to gluconeogenesis [75].

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 [69,73].

Some other adjuvant therapies were recommended to treat PT. The bovine somatotropin is reported as having therapeutic [77] and prophylactic [78] relevance in sheep and goats, but the mechanism of action remains poorly elucidated, and clinical use remains limited. The oral supplementation of L-carnitine ameliorated the immune response and lipid metabolism in goats [79].

A decrease in the richness and diversity of the ruminal microbiome is observed in ewes affected by PT, reducing the ability to produce volatile fatty acids [80]. A similar pattern was observed in the fecal microbiome of goats [81]. These aspects emphasize the importance of quickly reestablishing the gut microbiome of affected animals by improving the intake of an adequate diet.

Several therapeutic options of PT were recently reviewed by Bayne [82].

2.5. Prevention

The prevention of hyperketonemia is based, in the first instance, on the effective supply of a balanced diet in nutrients and energy density. 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 dairy 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 h a day, causing sub-acute ruminal acidosis [82,83]. 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) [82] 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 [84].

Despite the semiquantitative determination of some metabolites in milk (e.g., BHBA), the sample analysis is performed off-site at a laboratory, and even some on-farm handheld devices have been studied, such as BHBA meters for ketotic ewes [85] and does [86]. These handheld devices are based on electrochemical technology, allowing an accurate

mensuration of BHBA in blood samples in late pregnancy in ewes [87] (including subclinical PT [88] and does [86]. Nonetheless, when blood glucose levels are measured, it was reported that the distinction between normo and hypoglycemia is not suitable [86]. New sensors and algorithms are continuously under research and validation for use in small ruminants, e.g., Brobst et al. [89] (amperometric-based glucose biosensor) and Boileau et al. [90], for glucose and creatine in does, respectively. Biochemistry analysis seems to be the complement of the decision tree given by the mentioned threshold and composite indices for the effective implementation of precision medicine.

Another approach for herd health management of metabolic diseases is based on the combination of sensor data and health monitoring, such as described in dairy cows Sturm et al. [91], but this approach remains incipient, and more applied research is required. In a recent review, Alipio and Villena [92] described biosensors and intelligent wearable devices for monitoring cattle health. Some of them that combine rumination time and physical activity or even feeding behavior are reliable in detecting metabolic diseases. After validation, these systems may be translated to sheep and goats (e.g., [93,94]). Specific monitoring systems, based on sensing, Internet of Things and machine learning have been studied to improve small ruminants' welfare [95–97]. These last systems allow an automatization of surveillance and detection of abnormalities at individual and group levels. The readaptation of these systems for health monitoring can also contribute to the early detection of metabolic and other periparturient diseases in individuals and to their control and prevention in specific groups or flocks. Moreover, the interrelationships between animal well-being and animal health or animal production are demonstrated in domestic ruminants [98,99], although integrated approaches are required [100].

Omics and metabolomics are other promising tools driving the understanding of the molecular mechanisms of these pathologies for better medicine precision and prevention. Despite the relationship between gut microbiome and metabolomes (see [80,81]), the research on molecular metabolic mechanisms, the discovery of new genes related to fertility and fat metabolism (see Ji et al. [27]) can be used to predict animals at risk, etc.

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 are also observed in extensive production systems.

Subclinical and clinical hypocalcemia can be considered dependent on 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 [101].

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 [102]. Normal serum calcium (Ca) levels range from around 2.2 to 2.9 mmol/L (8.9–11.7 mg/dL in cattle), 2.8–3.2 mmol/L for sheep and 2.2–3.05 mmol/L for goats [54,60]. Its diffusing ionizable fraction (Ca^{++}) represents about half of the total calcium in serum. 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 mainly after parturition (up to 8 weeks). The fetoplacental mass is larger and the udder is smaller in pregnant ewes than in cows, mainly in multiple pregnancies [103]. Hypocalcemia is more likely to occur in does with high production levels or multiple fetuses, in which calcium concentration in milk is approximately 32.5 mmol/L (130 mg/dL) [60,104]. 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 [105] during the first week [106].

The clinical incidence of hypocalcemia is generally less than 5%. However, severe outbreaks may involve up to 30% of the flock [106,107]. Mortality can reach 90% of untreated animals [106]. Older animals (4–6 years) are considered more susceptible due to their lower capacity to regulate intestinal absorption and bone mobilization of calcium [108,109]. Sakhaee et al. [110] reported a total prevalence of 24.2% of subclinical hypocalcemia in Saanen and Beetal dairy goats. In this last study, hypocalcemia was observed in 6.8% and 39.4% of does carrying singletons and multiple fetuses, respectively. Other relevant risk factors associated with the most susceptible periods precipitate the occurrence of the disease, as reported in Table 5.

Table 5. Risk factor of hypocalcemia in ewes and does [108,111].

Risk factor
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 (<i>Beta vulgaris</i>), and alfalfa leaves (<i>Medicago sativa</i>)
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 handling, weather changes)

3.2. Etiopathology

The thresholds to define subclinical and clinical hypocalcemia are 2 mmol/L and 1.1 mmol/L of total serum calcium and Ca^{++} , respectively [110,111].

Abrupt change in feed or fasting (e.g., transportation) can cause 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 [112,113]. Also, magnesium plays a relevant role in supporting adequate production of parathormone, especially in the presence of moderate hypocalcemia [114].

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 [103] (Figure 2). 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 [108].

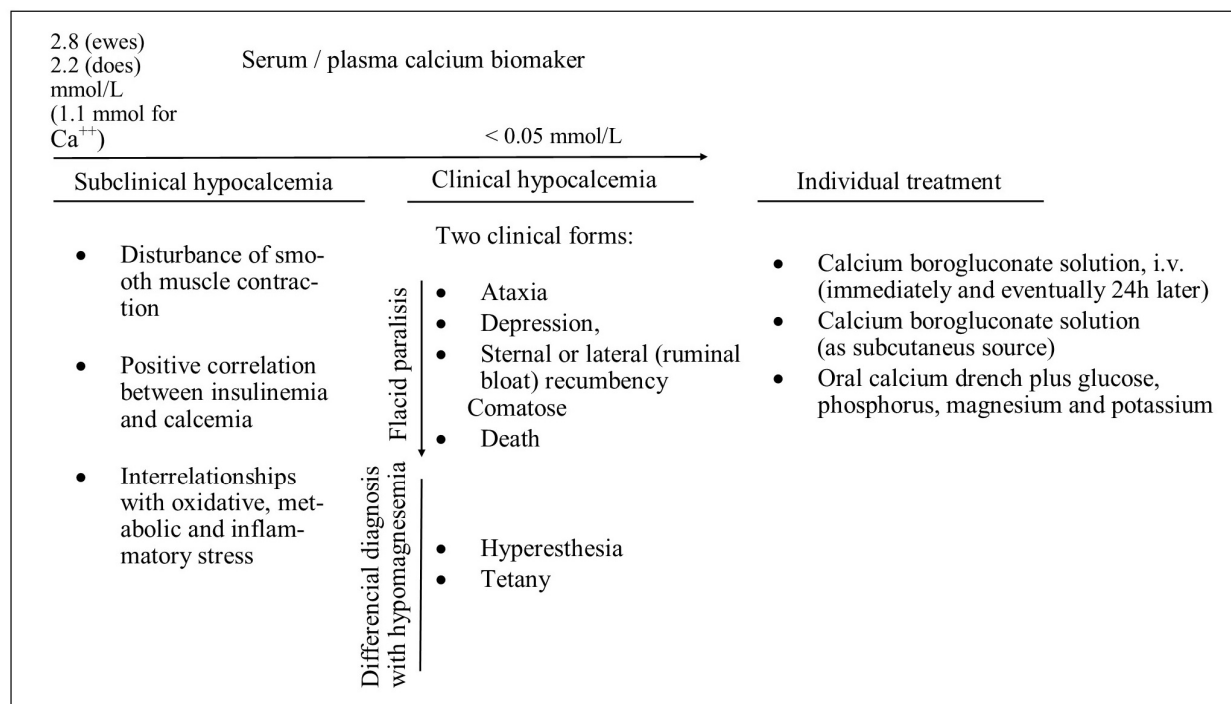


Figure 2. Diagram of diagnosis and therapeutic procedures of hypocalcemia in small ruminants.

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

A significant ($p < 0.001$) high coefficient of determination between serum magnesium ($R^2 = 0.76$), potassium ($R^2 = 0.68$), and inorganic phosphorous ($R^2 = 0.86$) concentrations sampled 10 days before kidding and postpartum serum calcium concentration on 1–2 days after kidding, were observed [110]. This multiple linear regression model is a candidate to serve as composite indices to predict postpartum hypocalcemia in goats measuring other microminerals in antepartum.

3.4. Treatment and Prevention

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

Prevention involves controlling risk factors and meeting 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) [115]. 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 [116,117]. 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. Handheld

devices to measure blood calcium on-farm were recently evaluated in dairy cows, but their accuracy remains low [118,119].

4. Hypomagnesemia

Some synonyms of hypomagnesemia are hypomagnesaemic tetany, grass staggers, wheat pasture poisoning, and milk or lactation tetany, denoting its symptoms or occurrence. Other than causing these specific clinical forms, magnesium also stabilizes blood glucose and calcium levels throughout the transition period [120].

4.1. Epidemiology

Older animals reared under the 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 [121]. However, this condition can also occur in fast-growing lambs or kids fed with replacement milk. A simple magnesium deficiency in the diet or any disorder causing a reduced availability and absorption of magnesium may lead to this unbalance.

4.2. Etiopathology

For instance, at the 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 [106,122].

Ionized magnesium (Mg²⁺) is mainly absorbed through rumen epithelial cells by two uptake mechanisms (potential-dependent and potential-independent). Other ionized molecules, such as high concentrations of NH₄⁺ and K⁺ or an increase of ruminal pH, can decrease the absorption of magnesium, contrary to high concentrations of short-chain fatty acid produced by ruminal microbiota [123].

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 (Figure 3) [124].

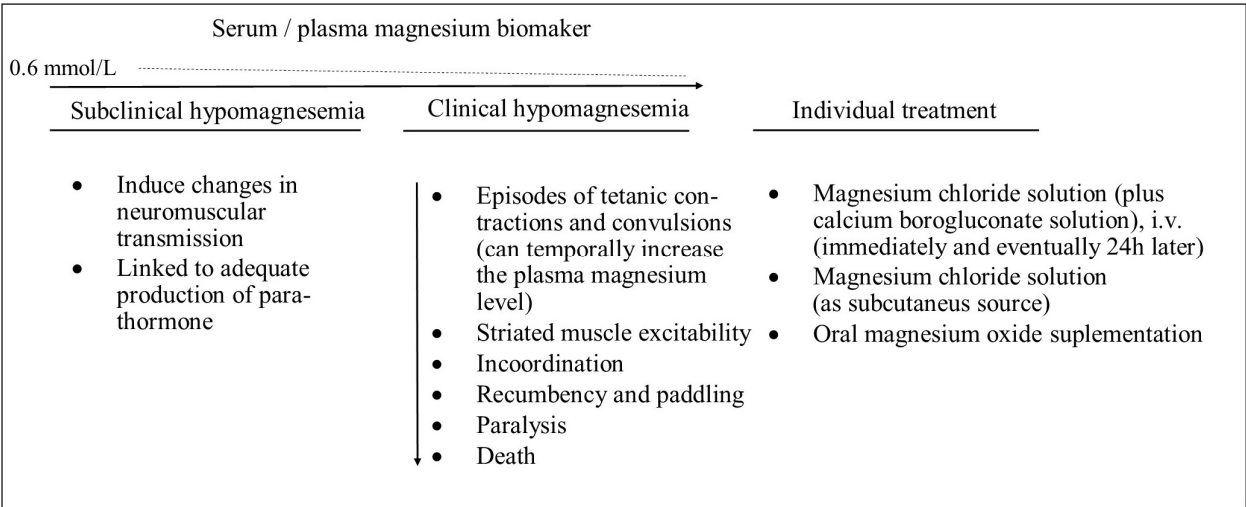


Figure 3. Diagram of diagnosis and therapeutic procedures of hypomagnesemia in small ruminants.

Serum or plasma magnesium can be measured to diagnose hypomagnesemia, as previously mentioned. Nonetheless, even if the threshold of 0.6 mmol/L is considered, the blood magnesium concentration can increase after an episode of tetanic contractions. In this situation, the measurement of magnesium concentration from cerebrospinal fluid can be 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 h) subcutaneously or in oral supplements to avoid relapses [125].

Prevention is mainly associated with magnesium salt supplementation (which is poorly palatable) up to 0.6% of dry matter during periods of greatest risk, namely from late pregnancy through early lactation [122,126]. 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. Integrated Prevention Plan for Metabolic Diseases

Since ketosis, hypocalcemia, and hypomagnesemia are interlinked, an integrated plan to control and prevent these metabolic diseases is the most appropriate clinical approach. Most of the procedures are based on nutritional management, animal handling (stressful factors), and biochemical sample evaluation, mainly during prepartum. Balanced diets are the major key factor in preventing metabolic diseases.

The risk of underfeeding is accentuated mainly from mid-pregnancy and in dams carrying multiple fetuses. As a consequence, maternal (chronic) undernutrition occurs [127]. Also, during early pregnancy, an unbalanced diet can improve embryonic mortality. This last aspect has a special economic relevance for meat-purpose breeds. In fact, the herd health program for metabolic diseases needs to incorporate the procedures throughout the production cycle. It should be designed according to the species, breed, production system, and production purpose. These plans incorporate both precision and population (group) medicine. Several based protocols of prevention are given in scientific literature. See Crilly et al. [128] for ewes in grazing production systems or the recent review on sheep and goats by Mongini et al. [13]. Several procedures regarding nutritional management and animal handling are summarized in Table 6.

Metabolic profiling consists of the evaluation of specific metabolites/biomarkers in a random sample selection of the population, even if the sample selection is previously structured (e.g., pregnant ewes and does 4–6 weeks antepartum). This is a herd-based diagnostic/preventive tool, allowing management and clinical decisions to reduce the incidence of disease when interpreted with other data sets of the farms [129,130]. Several metabolic profiles can be made according to the objective of the herd health plan, e.g., small ruminant chemistry (similar to a general chemistry panel), clinical metabolic, and metabolic profiles (see Hernandez et al. [131]).

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Table 6. Integrative measures to prevent metabolic diseases in periparturient ewes and does.

Nutritional Management
• Dietary apport: accomplish with nutrient and energy requirements for maintenance according the female body weight, and for production (fetuses and milk yield) [5,132]. • Basal diet bromatological analysis (e.g., grasses, silage, hay) should be performed when changing (or, in alternative, every six months) and balanced, according to the different production level of the animals. • Apport adequate dietary calcium throughout lactation (dairy) and gestation (meat). Special care is needed due to the low vitamin D dietary apport during winter season (less solar exposition) or confined animals to mitigate hypocalcemia [133]. Dietary magnesium should not exceed 0.4% of dry matter with a recommended potassium to magnesium ratio of 3.8–4:1 (2% potassium), sometimes with additional magnesium in mineral supplement [134]: High potassium levels (e.g., use of potassium fertilizers in pasture) reduce magnesium ruminal absorption. • High-risk pastures: avoid young grasses (low magnesium, sodium and calcium levels and high potassium levels mainly for cereal crops), grass fertilization with potassium, presence of oxalates (e.g., <i>Oxalis</i> spp., <i>Rumex</i> spp., <i>Chenopodium</i> spp. in pasture) causing calcium chelation in rumen and animal fluid. • Avoid alkaline diets, high in sodium and potassium, and low in sulphate and chloride. Use of acidogenic diets (dietary cation-anion difference > -50 mEq/kg; ideally > -100 mEq/kg) for high-producing animals at least for dairy goats [135]. The acidogenic diet can be apported during the last 10–15 days antepartum to provoke a transient metabolic acidosis in dairy animals, especially in flocks presenting high incidence of hypocalcemia. Restriction of calcium intake and metabolic acidosis induce urinary Ca^{++} excretion stimulating parathormone secretion [136]. Urine pH evaluation is required to monitoring metabolic acidosis status. Inconsistent results can be observed mainly in ewes at pasture [101,137], where the cation-anion difference of grass can significantly vary. Moreover, anionic salts (sulphates and chlorides-based) are unpalatable can reduce feed intake, mainly for high amounts of supplementation). The prepartum timeline can disagree for prepartum hypocalcemia (eg., meat sheep), when the demand of calcium is mainly required by fetuses (mainly for meat purpose). Nonetheless, it antepartum application can be useful for lactating ewes [138]. • Sudden dietary changes or other stressors should be avoided during late gestation. Sudden, short and complete fast of dams with normal BCS are normally associated with environmental stressful factors. Abrupt dietary changes primarily cause digestive disorders with repercussion in nutrients' absorption. A transition dietary period of 7–15 days is usually recommended. • Prevent or mitigate females to loss or gain excessive body weight or BCS (± 1 point on a 0–5 scale) considering fetal growth and milk yield throughout pregnancy and lactation. A BCS between 3.0 and 3.5 at parturition. Low and high BCS are associated with high levels of BHBA and PT [13,84].
Animal handling
• A flock breeding plan is needed. By day 50 of pregnancy, the number of fetuses should be evaluated by ultrasonography examination to make the nutritional adjustments according to singleton and multiple pregnancy (meat). • In dairy, the formation of two groups according to the level of production should be carried out for high-producing animals. • Keep an appropriate age structure of the flock. The older females (>3 years old) have more risk to present metabolic diseases. Involuntary (e.g., diseases, infertility) and voluntary (e.g., old age, low production, low fertility) culling should be evaluated to timely introduce new animals. Typically, an annual culling rate of around 20% is desirable to maintain a stable average age structure of the flock without increasing farm size. • Avoid (long) transportation of animals during late pregnancy. • Maintain animals in appropriate health and welfare conditions. Implement herd health programs for the main diseases and breeding; concomitant diseases such as Johne's disease and liver fluke increase the risk of PT [128]. Provide accommodation especially during adverse environmental weather, for grazing animals. • Early detection and treatment of metabolic diseases.

Table 6. Cont.

Metabolic profiling for periparturient metabolic diseases [131]
• BHBA, glucose, NEFA, • Creatinine, AST, GGT, ALP and CK enzymes, • Calcium, phosphorus and magnesium), • Total proteins (including albumin and globulin), serum urea nitrogen, • Electrolytes (sodium and potassium).

Most of the studies and clinical diagnoses of PT and LK consider the serum or plasma BHBA levels as the basal indicator. However, these manifestations of energetic and lipid metabolism disruption are complex, involving several organs, compartments, and body systems. At the herd level, the BHBA threshold appears to still be the most widely and accurately used indicator to take management decisions (0.8 and 1.1 mmol/L for ewes carrying singletons or multiple fetuses, respectively) [139]. At the individual level, special attention should be given to diagnostic biomarkers that also serve as prognoses. This information is crucial to deciding the therapeutic option, mitigating unnecessary economic losses related to the treatment, avoiding unnecessary animal suffering, and improving dams and offspring survival.

Finally, it should be noted that the advance on artificial intelligence is currently incipient and timeline unpredictively. Nonetheless, several advanced algorithms are described in dairy ruminants' welfare, health, and production, such as those reviewed by Neethirajan [140]. Algorithms and large learning models have been reported in different circumstances or using different devices, e.g., epidemiology, disease surveillance, and genomics [140], heat stress [141], rumen boluses (temperature, ruminal activity, and pH ruminal sensors) [142,143]. These examples will elucidate the potential application of artificial intelligence-based systems, which are transversal to all technical and scientific subjects.

6. 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 pregnancies.

Several diagnostic and prognostic biomarkers have been studied and applied in field conditions for clinical approaches of affected animals. Nonetheless, the large broad of factors influencing the surge and course of ketosis, someone poorly elucidated (e.g., pathophysiological mechanisms, insulin resistance, oxidative stress) cause limitations to their effective use and misinterpretation of the results in some circumstances. In recent years, new metabolites mainly related to inflammation and oxidative stress (see Table 2) were evaluated. However, the determination of cut-offs, such as the one reported in Table 1, is fundamental to interpreting their clinical value. In fact, a holistic approach regarding all these metabolic issues to better define the biomarkers and their cutoffs or their combined indices is required.

Furthermore, in this review, three distinct but complementary clusters to manage metabolic diseases were identified:

1. The improvement of (new) handled devices to quickly, ease, and accurately measure some biomarkers on-farm. Currently, the semi-quantification of BHBA is feasible, but the accurate quantification of glucose or calcium remains poor.
2. Individual and collective sensing. Several sensors were developed mainly for reproduction and animal welfare purposes. One's, e.g., rumination time, physical activity, and feeding behavior, can also be readapted and used to monitor individuals. Artifi-

cial intelligence algorithms can be introduced to early predict individuals or animal groups at risk, mainly in large flocks.

3. Internet of Things. Connect, integrate, and process the data from various sensors, distinct sensing, and automatic multi-target tracking in the cloud.

The feasible combination of sensors and algorithms at the engineering level will probably be the next disruptive step toward precision and population medicine. Health monitoring integrating information from different sources (animal health, risk factors, environment, nutrition, and feed analysis) converging into a real-time central database can enable predictions and decisions to improve the efficiency of animal health, welfare, and production during the periparturient period.

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