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Ketosis in ruminants; Acetonemia in cattle; Ketonemia

Pregnancy toxemias in sheep

Ketosis is a common disease of adult cattle. It typically occurs in dairy cows in early lactation and is most consistently characterized by partial anorexia and depression. Rarely, it occurs in cattle in late gestation, at which time it resembles pregnancy toxemia of ewes.

In addition to inappetence, signs of nervous dysfunction, including pica, abnormal licking, incoordination and abnormal gait, bellowing, and aggression are occasionally seen.

Etiology:

Glucose metabolism in ruminants:

The maintenance of adequate concentrations of glucose in the blood is critical to the regulation of energy metabolism.

The ruminant absorbs very little dietary carbohydrate as hexose sugar because dietary carbohydrates are fermented in the rumen to short chain fatty acids, principally acetate (70%), propionate (20%) and butyrate (10%). Consequently glucose needs in ruminants must largely be met by gluconeogenesis.

Propionate and amino acids are the major precursors for gluconeogenesis with glycerol and lactate of lesser importance.

Propionate:

Is produced in the rumen from starch, fiber and proteins. It enters the portal circulation and is efficiently removed by the liver, which is the primary glucose – producing organ.

Propionate is the most important glucose precursor; an increased availability can spare the hepatic utilization of other glucose precursors. And production of propionate is favored by a high grain inclusion in the diet.

Amino acids:

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The majorities of amino acids are glucogenic and are also important precursors for gluconeogenesis. Dietary protein is the most important quantitative source but the labile pool of body protein is also an important source. Together they contribute to energy synthesis and milk lactose synthesis as well as milk protein synthesis.

Dietary acetate:

Is transported to peripheral tissues and to the mammary gland and metabolized to long chain fatty acids for storage as lipids or secretion as milk fat.

Ketone formation:

Ketones arise from two major sources: Butyrate in the rumen and mobilization of fat.

A large proportion of butyrate produced by rumen fermentation of the diet is converted to beta - hydroxyl butyrate (BHBA) in the rumen epithelium and is absorbed as such.

Free fatty acids produced from the mobilization of fat are transported to the liver and oxidized to produce Acetyl CoA and NADH.

Acetyl –CoA may be oxidized via the TCA cycle or metabolized to acetoacetyl –CoA. Its oxidation via the TCA cycle depends upon adequate supply of oxaloacetate from the precursor propionate.

If propionate, and consequently oxaloacetate, is deficient, oxidation of acetyl- CoA via the TCA cycle is limited and it is metabolized to acetoacetyl CoA and subsequently to acetoacetate and BHBA.

The ketones BHBA and acetoacetate can be utilized as an energy source. They are normally present in blood and their concentration is a result of the balance between production in the liver and utilization by the peripheral tissues.

Hepatic insufficiency in ketosis:

The uptake of fatty acids by the liver leads to a fatty liver.

Hepatic insufficiency has been shown to occur in bovine and ovine ketosis but it does not occur in all bovine cases.

It has been suggested that hepatic insufficiency occurs in these cows predisposed to ketosis by feeding in the dry period.

Since one of the reactions to hypoglycemia is mobilization of fat reserves and uptake of fat by the liver, some degree of hepatic insufficiency is to be expected as a secondary development of the disease

Role of insulin and glucagon:

The regulation of energy metabolism in ruminant is primarily governed by insulin and glucagon. Their counteracting effects play a central role in the homeostatic control of glucose.

Low insulin: glucagon ratio stimulates lipolysis in adipose tissue and ketogenesis in the liver.

Cows in early lactation have low insulin – glucagon ratios because of low blood insulin and are in a catabolic state.

Elevated ketones may stimulate insulin production and may act as a negative feedback.

Regulation is also indirectly governed by somatotropin, which is the most important determinant of milk yield in cattle and is also lipolytic.

Factors that decrease the energy supply to ruminants that increase the demand for glucose, or that increase the utilization of body fat as an energy source are likely to increase ketone production and ketonemia.

There is however considerable cow – to – cow and ewe to ewe variation in susceptibility to clinical ketosis.

Energy balance:

In high – producing dairy cows there is often a negative energy balance in the first few weeks of lactation.

The highest dry matter intake does not occur until 8- 10 weeks after calving but peak milk production is at 4-6 weeks and energy intake may not keep up with demand.

In response to a negative energy balance and low serum concentrations of glucose and insulin , cows will mobilize adipose tissue

with consequent increases in serum concentrations of non – esterified fatty acids and BHBA.

The hepatic mitochondrial metabolism of fatty acids, promotes both gluconeogenesis and ketogenesis.

Cows partition nutrients during pregnancy and lactation and are in a lipolytic stage in early lactation.

Cows are at risk for ketosis during this period. Similarly the energy requirements in late pregnant twin – bearing ewes may place them in alipolytic status.

Etiology of bovine ketosis:

It is common in heavily producing cows in the post- calving period. This is because high yielding cows in early lactation are in negative energy balance and are sub clinically ketotic as a result.

Ruminants are particularly vulnerable to ketosis because although very little carbohydrate is absorbed as such, a direct supply of glucose is essential for tissue metabolism, particularly the formation of lactose.

The utilization of volatile fatty acids for energy purpose is also dependent upon a supply of available glucose.

This vulnerability is further exacerbated, particularly in the cow, by the tremendous rate of turnover of glucose.

In the period between calving and peak lactation the demand for glucose is increased and cannot be completely restrained.

Cows will reduce milk production in response to a reduction of energy intake, but this does not follow automatically or proportionately in early lactation because hormonal stimuli for milk production overcome the effects of reduced food intake.

Under these circumstances lowered blood glucose levels results in lowered blood insulin.

Long chain fatty acids are released from fat stores under the influence of both low blood insulin – glucagon ratio and the influence of high somatotropin concentration, and this leads to increased ketogenesis.

Subclinical ketosis

Elevated concentrations of blood ketones without clinical disease, subclinical ketosis, occur more commonly than clinical ketosis and have significant economic importance.

Various studies have shown that subclinical ketosis is common in high producing cows 2-7 weeks post partum, with recorded prevalence ranging from 7-34%. It takes only a small additional nutritional or metabolic insult for these to develop clinical ketosis.

Epidemiology

Ketosis in cattle

Occurrence

Ketosis is a disease of dairy cattle. It occurs mainly in animal housed during the winter and spring months and is rare in cows that calve on pasture. The occurrence of the disease is very much dependent upon management and nutrition and varies between herds.

Animal and management risk factors:

The diseases occur in the immediate post parturient period with 90% of cases occurring in the first 60 days of lactation.

Regardless of specific etiology it occurs most commonly during the first month of lactation, less commonly in the second month, and only occasionally in late pregnancy.

Cows of any age may be affected but the disease increases from a low prevalence at the first calving to a peak at fourth.

Cows with twins are also at risk for ketosis in the terminal stages of pregnancy.

Economic significance:

The economic effect of the disease is considerable. Without treatment, the case – fatality rate approaches 100%.

Clinical and subclinical ketosis is one of the major causes of loss to the dairy farmer.

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In rare instances the disease is irreversible and the affected animal's dies, but the main economic loss is due to the loss of production while the disease is present and failure to return to full production after recovery.

Both clinical and subclinical ketosis is accompanied by decreased milk yields and lower milk protein and milk lactose.

Pathogenesis:

Bovine ketosis:

Hypoglycemia and ketonemia may both exert an effect on the clinical syndrome .hypoglycemia is the predominant factors.

In most field cases the severity of the clinical syndrome is also roughly proportional to the degree of ketonemia.

Acetoacetic acid is known to be toxic and probably contributes to the terminal coma in diabetes mellitus in man.

The nervous signs are thought to be caused by the production of isopropyl alcohol , a break down product of acetoacetic acid in the rumen , although the requirement of nervous tissue for glucose to maintain normal function may also be a factor in these cases.

The pathogenesis of bovine ketosis is incompletely understood, but requires the combination of intense adipose mobilization and a high glucose demand.

Both of these conditions are present in early lactation, at which time negative energy balance lead to adipose mobilization and milk synthesis creates a high glucose demand.

Adipose mobilization is accompanied by high blood serum concentrations of non esterified fatty acids (NEFA).

During period of intense gluconeogenesis, a large portion of serum NEFA is directed to ketone body synthesis in liver. Thus, the clinicopathologic characterizations of ketosis include high serum concentrations of NEFA and ketone bodies and low concentrations of glucose.

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In contrast to many other species cattle with hyperketonemia do not have concurrent acidemia.

The serum ketone bodies are acetone, acetoacetate, and beta – hydroxyl butyrate (BHB).

There is speculation that the pathogenesis of ketosis cases occurring in the immediate post partum period is slightly different than that of cases occurring closer to the time of peak milk production.

Cases of ketosis in very early lactation are usually associated with fatty liver. Both fatty liver and ketosis are probably part of a spectrum of conditions associated with intense fat mobilization in cattle.

Ketosis cases occurring closer to peak milk production , which usually occurs at 4- 6 wk post partum , may be more closely associated with under fed cattle , experiencing a metabolic shortage of gluconeogenic precursors than with excessive fat mobilization. .

Epidemiology

All dairy cows in early lactation (first 6 wk) are at risk of ketosis. Cows with excessive adipose stores (body condition score ≥ 3.75 out of 5.0) at calving are at increased risk of ketosis, compared with those with lower body condition scores.

Lactating cows with hyperketonemia (subclinical ketosis) are at increased risk of developing clinical ketosis, compared with cows with lower serum BHB concentrations.

Types of bovine ketosis

It can be stated that clinical ketosis occurs in ruminants when they are subjected to demands on their resources of glucose and glycogen that cannot be met by their digestive and metabolic activity.

Classification of the disease

1. Primary ketosis (production ketosis)
2. Secondary ketosis
3. Alimentary ketosis
4. Starvation ketosis

5. Ketosis due to specific nutritional deficiency ,

Primary ketosis (Production ketosis):

This is the ketosis of most herds, the so-called estate acetonemia. It occurs in cows in good to excessive body condition that have high lactation potential and are being – fed good quality rations.

Secondary ketosis:

This occurs where other disease results in a decreased food intake. The cause of the reduction in food intake is commonly the result of abomasal displacement, traumatic reticulitis, metritis, mastitis, or other diseases, common to the post partum period.

A high incidence of ketosis has also been observed in herds affected with fluorosis.

An unusual occurrence³ reported was an outbreak of acetonemia in a dairy herd fed on a ration contaminated by a low level (9.5 ppm) of lincomycin, which caused ruminal microbial dysfunction.

Alimentary ketosis:

This form is due to excessive amounts of butyrate in silage and possibly also due to decreased food intake resulting from poor palatability of high butyrate silage. Silage made from succulent material may be more highly ketogenic than other types of ensilage because of its higher content of preformed butyric acid. Spoiled silage is also cause and toxic biogenic amines in silage, such as putyrssin may also contribute.

This type of ketosis is commonly subclinical but it may predispose to the development of production or primary ketosis.

Starvation ketosis:

This occurs in cattle that are in poor body condition and that are fed poor – quality feedstuffs. There is a deficiency of propionate and protein from the diet and a limited capacity of gluconeogenesis from body reserves. Affected cattle recover with correct feeding.

Ketosis due to specific nutritional deficiency:

Specific dietary deficiencies of cobalt and possibly phosphorus may also lead to a high incidence of ketosis.

This may be due in part to a reduction in the intake of total digestible nutrients, but in cobalt deficiency the essential defect is a failure to metabolize propionic acid into the tricarboxylic acid (TCA) cycle.

Clinical findings:

Bovine ketosis

Two major forms of bovine ketosis are described – wasting and nervous

The wasting form:

Is the most common of the two and is manifested with a gradual but moderate decrease in appetite and milk yield over 2-4 d.

The pattern of appetite loss is often unusual in that the cow first refuses, to eat grain, then ensilage but may continue to eat hay.

The appetite may also be depraved. Body weight is lost rapidly, usually at greater rate than one would expect from the decrease in appetite.

Farmers usually describe affected cows as having a woody appearance due to the apparent wasting and loss of cutaneous elasticity due presumably to disappearance of subcutaneous fat.

The feces are firm and dry.

The cow is moderately depressed and the hangdog appearance and disinclination to move and to eat may suggest the presence of mild abdominal pain. The temperature, and the pulse and respiratory rates are normal.

A characteristic odor of ketones is detectable on the breath and often in the milk. Very few affected animals die.

In wasting form, nervous signs may occur in a few cases but rarely comprise more than transient bouts of staggering and partial blindness.

The nervous form signs are usually bizarre and begin quite suddenly.

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The syndrome is suggestive of delirium rather than of frenzy and the characteristic signs include:

Walking in circles.

Straddling or crossing of the legs.

Head pushing or leaning into the stanchion.

Apparent blindness

Aimless movements and wandering

Vigorous licking of the skin and inanimate objects.

Depraved appetite 'chewing movements with salivation

Hyperesthesia may be evident, the animal bellowing on being pinched or stroked.

Moderate tremor and tetany may be present and there is usually an in coordinate gait.

The nervous signs usually occur in short episodes which last for 1 or 2 h. and may recur at intervals of about 8-12 h. affected cows may injure themselves during the nervous episodes.

Subclinical bovine ketosis;

Many cows that are in negative energy balance in early pregnancy will have ketonuria without showing clinical signs. But show decrease productivity including depression of milk yield and a reduction in fertility.

In cows maintained in confinement stalls, reduced feed intake is usually the first signs of ketosis. Cows with ketosis often refuse grain before forage.

In group - fed herds, reduced milk production, lethargy and an empty appearing abdomen are usually the signs of ketosis noticed first.

On physical examination cows are a febrile and may be slightly dehydrated. Rumen motility is variable, being hyperactive in some cases and hypoactive in others.

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CNS disturbances are noted in a minority of cases. These include abnormal licking and chewing, with cows sometimes chewing incessantly on pipes and other objects in their surroundings.

In coordination and gait abnormalities occasionally are seen, as are aggression and bellowing.

Diagnosis:

The clinical diagnosis of ketosis is based on presence of risk factors (early lactation), clinical signs and ketone bodies in urine and milk).

Common concurrent diseases with ketosis include: displaced abomasums, retained fetal membranes, and metritis.

Rabies and other CNS diseases are important differential diagnosis.

Cow – side tests for the presence of ketone bodies in urine or milk are critical for diagnosis.

Clinical pathology:

Hypoglycemia, ketonemia, and ketonuria are characteristic of the disease.

Cattle blood glucose levels are reduced from the normal of approximately 50mg \ dl to 20-40 mg \ dl. In cattle and sheep.

Ketosis secondary to other disease is usually accompanied by blood glucose level above 40 mg \ dl often above normal

Ketones :

Blood ketone levels are elevated from a normal of up to 10 mg \dl to 10-100 mg \dl. The levels are high also in secondary ketosis but bare rarely above 50 mg \ dl.

Urine ketosis:

Quantitative estimation of urinary ketones may be unsatisfactory because of the wide variations that occur depending upon the concentration of the urine.

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In clinically normal cattle, urinary ketones may be as high as 70 mg \ dl although they are usually lower than 10 mg \dl.

Level of 80- 1300 mg \dl the presence of ketosis which may be primary or secondary.

Milk ketone

Level are rather less variable , ranging from a normal of 3 mg \ dl up to an average level of 40 mg \dl in cows with ketosis.

Cowside tests

Are based on color reaction of ketone bodies and may be conducted on milk or urine.

Milk usually tested with sodium, nitroprusside in the well of a porcelain plate.

Commercial tablets or dip sticks are available for testing urine.

Pregnancy toxemia in ewes ; twin lamb disease , pregnancy ketosis
,sleeping ewe disease

In sheep, the initial changes are similar to those found in cattle but the sequel is not.

Hypoglycemia can be used as a diagnostic aid in the early stages of the disease but is of limited value. Ketonemic and ketonuria are constant and serum beta – hydroxyl butyrate concentrations are in excess of 3 mmol\ l.

Sheep develop a severe metabolic acidosis, renal failure, with a terminal uremia, and become dehydrated.

In contrast to cattle, liver function tests are abnormal.

Elevation of plasma cortisol occurs in pregnancy toxemia and concentration above 10 mg \ ml is indicative of pregnancy toxemia.

The disease in sheep is manifested with encephalopathy and is frequently not reversible unless treated in the early stages.

The onset of clinical signs is always preceded by hypoglycemia and hyperketonemia.

The cause of the encephalopathy is not certain but it is probable that it is a hypoglycemic encephalopathy resulting from hypoglycemia in the early stages of the disease.

In affected ewe, there is an abnormally high level of cortisol in plasma. The research has suggested that adrenal steroid diabetes contributes to the pathogenesis.

Renal dysfunction is also apparent in the terminal stages of ovine ketosis, and may also contribute to the development of clinical signs and the fatal outcome.

Etiology of ovine ketosis

Hypoglycemia and hyperketonemias are the primary metabolic disturbances in ovine ketosis as they are in the bovine disease.

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In sheep, the precipitating causes are the energy demands of the conceptus in the latter part of pregnancy.

There are some biochemical differences between the two diseases e.g. an elevation of plasma cortisol levels and significant hepatic dysfunction in pregnancy toxemia. Furthermore, in the terminal stages, the biochemical pathogenesis of the two diseases appears to be quite dissimilar.

The most important etiological factor in pregnancy toxemia is a decline in the plane of nutrition during the last 2 months of pregnancy, particularly in ewes that are carrying twins or triplets, and in ewes that have been well fed in early and mid- pregnancy.

It is probable that the difference between sheep depends upon the metabolic efficiency of the liver.

Ewes that are predispose to the disease have an ineffective gluconeogenic response to the continued , preferential demands for glucose by well- grown twin fetuses , resulting in hypoglycemia and the accumulation of ketone bodies and cortisol.

The elevation of plasma cortisol levels, has attracted attention because of is possible indication of adrenocortical involvement i8n causing the disease.

It seems more likely that the observed increase is in response to environmental and nutritional stresses, and possibly to failure by the liver to metabolize the cortisol.

Clinical Signs

Ovine ketosis

The earliest signs of ovine ketosis are separation from the group . failure to come up for feeding. Apparent blindness which is manifested by an alert beating but a disinclination to move.

The ewe will stand still when approached by attendants or dog and will turn and face them but make no attempt to escape.

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If it is forced to move, it blunders into objects and when an obstacle is encountered presses against it with its head.

Many affected ewes stand in water troughs all day and lap the water. Constipation is usual, the faces are dry and scanty and there is grinding of the teeth.

In the later stages, marked drowsiness develops episodes of more severe nervous signs occur but they may be infrequent and are easily missed.

In these episodes, tremors of the muscles of the head cause twitching of the lips, champing of the jaws and salivation and these are accompanied by a log - wheel type of clonic contraction of the cervical muscles causing dorsal flexion, or lateral deviation of the head, followed by circling.

The muscle tremor usually spread to involve the whole body and the ewe falls with tonic - clonic convulsions.

The ewe lies quietly after each convulsion and rises normally afterward but is still blind.

In the periods between convulsions there is marked drowsiness which may be accompanied by head pressing, the assumption of abnormal postures including unusual position of the limbs and elevation of the chin – the stargazing posture – and in coordination and falling when attempting to walk.

A smell of ketones may be detectable on the breath of the ewe.

Affected ewes usually become recumbent in 3-4 d. and remain in a state of profound depression or coma for a further 3-4 d.

Although the clinical course is shorter in fat ewes with pregnancy toxemia.

Fetal death occurs commonly and is followed by transient recovery of the ewes, but the toxemia caused by the decomposing fetus soon causes a relapse. Affected ewes commonly have difficulty in lambing.

Recovery may ensure if the ewe lambs or the lambs are removed cesarean section in the early stages of the disease.

In an affected flocks the disease usually takes the form of a prolonged outbreak , a few ewes become affected each day over a periods of several weeks .recovered ewes may subsequently show a wool break.

According to the broad circumstances of occurrence, the disease in sheep can be divided as to cause as either:

1. Primary pregnancy toxemia
2. Fat ewe pregnancy toxemia.
3. Starvation pregnancy toxemia
- Or 4. Secondary pregnancy toxemia.

Primary pregnancy toxemia

This is the most common manifestation and results in most flocks from a combination of a fall in the plane of nutrition during the latter half of pregnancy coupled with a short period of fast – in conjunction with a management procedure in late pregnancy such as crutching , shearing and drenching.

In some outbreaks the ewes have been moved onto better pasture during late pregnancy to prevent the occurrence of ketosis but it occurs because the ewes are unaccustomed to the type of feed and do not eat well , or because they are more exposed to bad weather and seek shelter rather than graze.

Cold, inclement weather and an absence of shelter also appear to, markedly increase the incidence.

Another common occurrence is when ewes are bred too early and the pasture is not sufficiently advanced to provide arising plane of nutrition in late pregnancy.

Occasionally a stress alone will induce the condition such as:

1. Transport in late pregnancy
2. Change in environment

Or 3. The housing of late pregnant sheep not used to being housed. fat ewe pregnancy toxemia":

This occur without a stress induction in ewes that are very well fed and are in an over fat condition in late pregnancy.

Fat ewes will experience a voluntary fall in food intake in late pregnancy due to the reduction of the rumen volume by the pressure of intra abdominal fat and the developing fetus.

Commonly there is concurrent hypocalcaemia.

Starvation pregnancy toxemia.

This occurs in ewes that are excessively thin. It is relatively uncommon but occurs in extensive grazing systems when there is prolonged drought and no alternative feed supply.

Secondary pregnancy toxemia:

This usually occurs as a sporadic disease as the result of the effect of an inter current disease such as a foot rot, which effects food intake.

Heavily worm infestation e.g. with *Haemonchous contortus*, would add a similar drain on glucose metabolism and increase the chances of development of the disease.

Goats

The disease occurs in goats during late pregnancy, where it is identical to ovine pregnancy toxemia, and also in lactating does, where it resembles bovine ketosis,

Goats exhibit greater dominant sub missive characteristics than sheep and this can result in lower food intake in submissive goats in groups that are hand fed.

Differential diagnosis:

Cattle

Wasting form

Abomasal displacement

Traumatic reticulitis

Primary indigestion

Cystitis and pyelonephritis

Diabetes mellitus.

Nervous form

Rabies

Hypomagnesaemia

Bovine spongiform encephalopathy.

Sheep

Pregnancy toxemia is usually suspected in late pregnancy, ewe which show nervous sign and die within 2-7 d.

Listeriosis

Cerebral abscess

Rabies

Treatment

Glucose (dextrose) IV injection of 500 ml of 50% solution of glucose results in transient hyperglycemic

Hormonal therapy

Glucocorticoides

Treatment in sheep

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Fluid, electrolytes, and glucose given over a prolonged period of time.

5-7 g glucose IV 6-8 times a day in conjunction with 20-40 units of zinc protamine insulin given IM every other day for 3 d.

Removal of fetus. Caesarian section.