The Pharma Innovation Journal 2022; SP-11(9): 610-616

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2022; SP-11(9): 610-616

www.thepharmajournal.com
Received: 27-06-2022
Accepted: 29-07-2022

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Post-partum metabolic diseases in cattle and buffalo: A review

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Abstract
The periparturient period is when cows are most susceptible to infections and metabolic problems, therefore nutritional management throughout the dry season may have an impact. Increased body tissue mobilisation, decreased plasma glucose levels, and increased plasma concentrations of non-esterified fatty acids (NEFA) and ketone bodies are all results of the endocrine changes and regulation that occur during calving. Immune competence and abnormal body mobilisation serve as fundamental rationals for metabolic and immune state and support the creation of markers for metabolic imbalance and the onset of diseases early on. The highest incidence of metabolic illnesses such milk fever, postpartum haemoglobinuria, and ketosis is connected with the transitional period between three weeks prepartum and three weeks postpartum. Metabolic blood profiles are frequently used to detect and signal metabolic disturbances and low productivity. Reduced milk production, an increased chance of delayed estrous, and lower conception rates are all symptoms of metabolic disorders.

Keywords: Metabolic, milk fever, ketosis, cattle, buffalo

Introduction
In the peripartum period, there is a correlation between depression of feed intake and metabolic disorders. The prevalence of metabolic problems in buffaloes associated to production or parturition is limited. (Purohit *et al*., 2013) [58]. These changes are likely noticeable because buffaloes produce less milk, which leads to a less severe negative energy balance during parturition (Grasso *et al*., 2004) [27] diminished blood stream lipid metabolization in buffalo at their peak lactation (Monteiro *et al*., 2012) [53] without any signs of fatty liver in the postpartum buffalo (Jalali *et al*., 2011) [38] and better utilization of minerals by buffalo from coarser roughages (Sebastian *et al.*, 1970) [63]. A series of diseases known as metabolic disorders of cattle affect dairy cows right after parturition. For dairy cows, the transition period is roughly 3 weeks prior to delivery through 3 weeks following delivery. During this time of transition, disease incidence and severity are at their highest phases when the immune system is compromised. Around the time of calving, metabolic and microbial diseases involve a disordered inflammatory response. Dairy cows must be monitored for changes in feed intake during the periparturient period since inadequate intake of dry matter is associated with numerous of postpartum diseases, such as ketosis, metritis and mastitis (Bareille *et al.*, 2003; Huzzey *et al.*, 2007) [5, 36].

Post parturient haemoglobinuria
In India, postpartum hemoglobinuria (PPH) represents a significant threat to milking buffaloes during late pregnancy and the first few months of lactation (Ghanem and El-Deeb 2010; Mahmood *et al*., 2013) [24, 47]. According to Durrani *et al.* (2010) [20] the prevalence was highest at the fifth lactation and lowest at the first. Acute intravascular hemolysis and severe anaemic anoxia make it highly lethal. Haemoglobinuria is the common problem in buffaloes specially fed on leguminous fodder during summer season (Jain *et al*., 2012) [37] possibly due to metabolic deficits during high milk yields (Choudhary *et al*., 2013) [12]. This condition has phosphorus deficiency as a constant finding, and treatment with sodium acid phosphate is effective in clinical situations (Pandey and Misra, 1987). Hypophosphataemia is anticipated to lead to a reduction in red blood cells, glycolysis, and ATP generation. Subnormal concentration of ATP predispose red blood cells to altered function and structure, a loss of normal deformability and increase in fragility and hemolysis with resulting hemoglobinaemia and hemoglobinuria (Khan and Akhtar, 2007) [42].

Due to decreased level of ATP, erythrocytes loose their deformability become rigid and ultimately leave the circulation due to decreased life span (Radostits *et al.*, 2007; Akhtar *et al.*, 2007b) [59, 1]. According to Mata and Bhardwaj (1985) hypothesis, phosphorus deficit in PPH buffaloes reduces the rate at which erythrocytes use glucose and produce ATP, which lowers their ability to synthesise glutathione and makes them more susceptible to the harmful effects of oxidative stress. Intravascular hemolysis is eventually caused by the oxidative stress that accompanies the lipid peroxidation of the red cell membrane. Although the specific pathophysiology of this condition is not entirely understood, risk factors for it include eating cruciferous plants, berseem saponin not getting enough phosphorus in your diet, having low levels of serum copper and selenium and having high levels of molybdenum. (Neto *et al*., 2007; Brechbuhl *et al*., 2008) [55, 10]. While an excess of molybdenum also lowers phosphorous content by interfering with its absorption and increasing its elimination through urine, low phosphorous diets with high calcium content cause hypophosphataemia by decreasing phosphorous absorption from the gastro-intestinal tract due to a wider ratio of calcium and phosphorous (Khan and Akhtar, 2007; Dua, 2009) [42, 15]. Additionally, hypermolybdenosis causes a decrease in copper, which decreases the activity of the copper-containing enzyme superoxide dismutase, a component of the erythrocytendefence mechanism against oxidative stress (Kahn and Line, 2005; Radostits *et al.*, 2007) [40, 59].

Clinical findings

Disease with haemoglobinemia as a primary clinical symptom anemia, hemoglobinuria and straining while urinating (Gupta *et al*., 2010) [29]. With the progression of anaemia, tachycardia, quick and shallow breathing, depression, and reduced milk production, mucous membranes becoming pale or icteric (Ghanem and El-Deeb, 2010) [24]. Increased heart rate and pulse rate may be seen (Akhtar, 2006; Gupta *et al.*, 2010) [3, 29]. Depending on the severity and length of the sickness, haemoglobinuric buffaloes produced urine that ranged in colour from red to dark red to coffee-colored (Akhtar, 2006) [3]. If the animal is left untreated, there is a gradual loss of body function, and recumbency is followed by death.

Diagnosis

The history of the recently calved animal and clinical symptoms are used to make the diagnosis. A blood analysis demonstrates a sharp decline in haemoglobin the number of total erythrocytes, and packed cell volume. Urine examined under a microscope reveals that there are no erythrocytes and is positive for the benzidine test. Low levels of 0.5-3.0 mg/dl of serum inorganic phosphorous (normal range: 4.0-7.0 mg/dl) are present. Numerous authors reported that during hemolytic crises, serum inorganic phosphorus levels are extremely low (0.13-0.49 mmol/l) (Ellison *et al*., 1986) [21].

Line of treatment

Following intravenous administration of 60 g of sodium acid phosphate dissolved in 300 ml of 5 percent dextrose, the same amount was then given orally twice daily for three days (Singh *et al*., 1989) [69]. Ascorbic acid at 5g per animal helps iron maintain a reducing state, reduce intravascular hemolysis, and reduce oxidative stress on red blood cells (Benerjee, 1998) [4]. It was successful to treat PPH in buffaloes by injecting botropase (10 ml/animal), a blood coagulant made from the venom of the snake *Bothrops jararaca*, which appears to have antifibrinolytic activity (Goel *et al*., 1988) [25]. For 5-7 days, oral supplements of monosodium phosphate, dicalcium phosphate, or 100 gm of bone meal should be administered daily. Additionally recommended are parenteral injections of copper (120 mg/cow). Tea leaves can be used as a supportive treatment along with toldimfos sodium (4-dimethyle 1-2 methyl phosphorus acid sodium salt) as an alternative to sodium acid phosphate therapy because of their astringent action, which helps to clear up urine staining (Durrani *et al.*, 2010) [20].

Prevention and control

Animals should be provided a balanced diet rich in minerals. After parturition mineral mixture should be given @ 50 g/day orally for 1 month. A decrease in the incidence of the disease is reported after copper supplementation of cattle in a copper-deficient area.

Milk fever

Milk fever is metabolic disease also known as parturient paresis, parturient apoplexy, calving paralysis and post parturient hypocalcaemia (Littledike *et al*., 1981) [46]. Most frequently develops within 48 hours after parturition, especially in high milk producing dairy cows. The incidence of milk fever is highest in jersey breed (Littledike *et al*; 1981) [46]. Over-conditioned cows (body condition score >3.5, in a scale of 1–5) are at increased risk of hypocalcaemia (Heuer *et al*., 1999) [33]. Ionized calcium levels in tissue fluids are decreasing which is the primary biochemical defect in this diesase. Clinical signs of milk fever include weakness, recumbency, shock and mortality. Diesase commonly occurs in 5-10 years age group and most marked in third to seventh parity (Singh and Singh, 2017) [70]. Dietary calcium intake influences both the mobilisation of calcium from bone and the absorption of calcium from the gut, which is regulated by 1, 25(OH)2D3. The efficiency of intestinal absorption and the mobilisation of calcium from bone both decline when dietary Ca concentration and total dietary calcium consumption rise. (Ramberg, 1995) [60]. In reaction to decreased blood Ca levels, the parathyroid glands release parathyroid hormone (PTH). PTH controls the kidney's ultimate hydroxylation of 25-hydroxycholecalciferol (25-hydroxy- D3) to 1, 25(OH)2D3. PTH speeds up the release of calcium from bone. Ten litres of colostrum produced at calving will lose 23 g of calcium in a single milking (Horst *et al*., 1997) [34].

Clinical findings

Three stages of milk fever in cattle are commonly recognized and described.

Stage 1(stage of excitement)

The cow is still standing at this point. At this stage, symptoms include ataxia, stiffness in the hind legs, normal to slightly elevated rectal temperature, hypersensitivity and muscular tremor in the head and limbs.

Stage 2 (stage of sternal recumbency)

The cow appears sleepy in sternal recumbency, frequently with the head turned into the flank or the neck twisted to the side ('S' posture) (Singh and Singh, 2017) [70]. Important findings at this stage include subnormal temperature, a noticeable increase in heart rate (about 80 bpm), a decrease in the absolute intensity of the heart sounds, a weak or

nonexistent pupillary light reaction, a weak arterial pulse, low venous pressure and ruminal stasis. A typical milk fever consequence is uterine prolapse.

Stage 3 (stage of lateral recumbency)
The cow is nearly unconscious and heart beat is elevated 120 beats per minute and pulse is barely audible. In this stage animal was in lateral recumbency due to bloat is common.

Diagnosis
The history of a recent parturition and clinical indicators are used to make the diagnosis. Adult cows typically have a calcium level of 8 to 12 mg/dl. In this condition is indicated by hypocalcemia (5 mg/dl) and high serum creatinine phosphokinase (CPK). Long-term lateral recumbency causes ischemic muscle necrosis and increases in the levels of the muscle enzymes aspartate aminotransferase (AST) and creatine phosphokinase (CPK) in the serum (AST).

Line of treatment
The best time for treatment is when the disease is still in its early stages. The incidence of the downer cow syndrome caused by persistent ischemic muscle necrosis increases with the amount of time between when the cow first gets recumbent and when it receives therapy. For cattle, 400-500 mL of 25% solution of calcium borogluconate is the usual dose for dairy cattle weighing 300-400 kg. Cows with milk fever exhibit a typical pattern of response to calcium borogluconate if the response is favorable, including:

1. Belching
2. Muscle tremor, particularly of the flanks and often extending to the whole body
3. Slowing and improvement in the amplitude and pressures of the pulse
4. Increase in the intensity of the heart sounds
5. Sweating of the muzzle
6. Defecation.

The slow intravenous method is used to provide 50% of the predicted dose, while the subcutaneous route is used for the remaining 50%. Giving a higher calcium dose intravenously is not beneficial (Doze *et al*., 2008) [13]. With initial calcium therapy, composite solutions comprising calcium, phosphorus, and glucose are advised for nonresponsive and recurrence cases (Sharma *et al*., 2009) [65].

Prevention and control
The incidence of hypocalcemia and milk fever in dairy cows can be significantly reduced by lowering the amount of absorbable food cations (Na, K, Ca, and Mg) and/or increasing the amount of absorbable dietary anions (Cl, sulphate, and phosphate) (Block, 1984) [9]. When fed to parturient cows, oral calcium formulations can significantly reduce the incidence of milk fever cases. It has been proposed that another crucial element in the emergence of milk fever is the Ca/P ratio. In the last month of pregnancy, feeding a high phosphorus/low calcium ration (3.3:1) may help prevent the condition. Prevention of milk fever also benefits from the administration of vitamin D and its metabolites.

Ketosis
Negative energy balance is the main metabolic disease known as ketosis, which is characterised by relatively high ketone body concentrations and a simultaneous drop in blood glucose levels. Dairy cows are particularly vulnerable to poor energy balance during late pregnancy and early lactation due to a significant increase in energy demand (Youssef *et al*., 2010) [75]. Within four weeks after parturition, cows that don't adjust well to negative energy balance (NEB) may experience hyperketonemia (clinical or subclinical ketosis). During this time, a significant amount of body fat is being used as energy to support milk production. This causes a marked mobilisation of lipids and a noticeable increase in circulating non-esterified fatty acids and ketone bodies in tissues and milk. (Herdt, 2000) [32]. Increases in the prevalence of postpartum disorders such as retained placenta, milk fever, metritis, mastitis, clinical ketosis, and displaced abomasum as well as decreased milk yield and reproductive performance, severe negative energy balance in the puerperal period are all linked to subclinical ketosis, which is defined by an elevated concentration of ketone bodies in the absence of clinical signs (Duffield *et al*., 2009; LeBlanc, 2010; McArt *et al*., 2012) [17, 44, 50]. These factors cause significant economic loss (Shin *et al*., 2015; Suthar *et al*., 2013) [67, 72]. According to Duffield *et al*. (1998) [18], subclinical ketosis can occur at a rate of 26 to 60% and clinical ketosis at a rate of 2 to 15% (Duffield, 2000) [16]. High yielding cows in India are more vulnerable to ketosis than the non-descript cows that produce less milk (Thirunavukkarasu *et al*., 2010) [73]. Early lactation after a late gestation has been linked to a high frequency of production disorders (Mulligan and Doherty, 2008) [54]. High NEFA or BHBA concentrations were reported to induce immune dysfunction, which in turn is a major component of inflammatory disease in the reproductive tract (LeBlanc, 2012) [45]. At calving, a body condition score (BCS) of 3.5 or higher was linked to an increased risk of ketosis. Dairy farmers suffer financial losses as a result of a high prevalence of clinical and subclinical ketosis due to decreased milk production and a fast decline in the milk's Solid Not Fat (SNF) composition (Tufani *et al*., 2011) [74]. The development of ketosis during the postpartum period may be characterized by a decrease in dry matter intake around parturition, an increase in glucose needs, and insufficient propionate synthesis during the early postpartum period (Drackley and Dann, 2005) [14]. Due to ketosis-induced hypoglycemia, lactose synthesis and milk output decline (Simensen *et al*., 1990) [68].

Clinical findings
There are two different types of symptoms: nervous and intestinal. Loss of appetite (Grohn *et al*., 1983) [28], a sharp decline in milk production (Mir and Malik, 2002) [52], selective feeding (Lean *et al*., 1991) [43], a lack of rumination (Hungerford, 1990) [35] constipation (Bihani, 2001) [8] and firm mucus-coated faeces are signs of the digestive type (Bhuin and Chakrabarti, 1993) [7]. The apparent atrophy and loss of skin flexibility caused by what is likely the removal of subcutaneous fat has given affected cows a woody look (Sharma, 2006) [64]. According to (Bihani, 2001) [8] urine, milk, and breath all exhibit an acetone-like odour,. Ketotic cows have been seen to exhibit neurotic symptoms such as hyperesthesia (Chakrabarti, 2006) [11], salivation (Sharma *et al*., 2004) [66] licking their faces continuously, trembling, and strange walking patterns. Ketosis, which is characterised by a decrease in feed intake and milk production, is brought on by the generation of a greater quantity of ketone bodies (BHBA) as a result of insufficient fatty acid oxidation in the liver (Duffield, 2011) [19].

Diagnosis

Diagnosis is based on the history of recent calving and clinical signs. Ketosis can be diagnosed by measuring the concentration of ketone bodies (β-hydroxybutyrate [BHBA], acetone and acetoacetate), intermediate metabolites of fatty acid oxidation present in blood, urine or milk. A definition of ketosis greater than 1,400 μmol of BHBA/L of serum and a cutoff of ≥200 μmol/L of milk resulted in a sensitivity of 59% and a specificity of 90% (Geishauser *et al*., 2000) [23].

Accurate diagnosis would require estimation of blood glucose and ketone levels however, in clinical practice the Ross modification of the Rothera test has been used and described to be reliable (Fox, 1971) [22]. The reagent consists of 99 g of ammonium sulfate mixed with 1 g of sodium nitroprusside. Approximately 1 g of this mixture is added to 5 to 7 ml of urine in a standard test tube and after dissolving 1 ml of ammonium hydroxide solution or a flake of sodium hydroxide is added. After keeping for 3 to 5 minutes, the test is read:

No color change : (negative)
Slight lavender : 1+
Deep lavender : 2+
Beet red or purple : 3+
Deep beet red or purple and opaque (strongly positive) : 4+

A milk BHBA test strip (Keto-Test) was used by the participating veterinarians for screening a milk sample from cows. The strip was dipped into the milk sample for 3 seconds, read after 1 minute and recorded according to the color scale provided with the test. The color scale shows 6 colors corresponding to nominal levels of 0, 50, 100, 200, 500, and 1,000 μmol of BHBA/L of milk. A recording of 100 μmol of BHBA/L of milk or higher was defined as ketosis (Berge and Vertenten, 2014) [6].

Line of treatment

A large number of studies have been undertaken to identify effective treatments and evaluate glucose precursors oral propylene glycol (PG), glucocorticoid, niacin, insulin, recombinant bovine somatotropin, butaphosphan, cyanocobalamin and combined therapies (McArt *et al*., 2011; Gohary *et al*., 2015; Nuber *et al*., 2016) [51, 26, 57]. Glucocorticoids have been used in ketosis treatment because of their ability to produce hyperglycemia as a result of changes in glucose use (Herdt and Emery, 1992) [31]. Steroids also block the effects of insulin, allowing for increased catabolism of fat and protein stores. Plasma concentrations of both glucose and insulin increase significantly about 48 hours after injection with dexamethasone (Jorritsma *et al*., 2004). Insulin is used in the treatment of ketosis because of the anabolic effects of the hormone (Hayirli, 2006) [30]. Insulin decreases fat breakdown, increases fat synthesis, and increases use of ketone bodies as energy sources, which should decrease the level and consequences of ketonemia.

Administration of vitamin B_{12} may increase gluconeogenesis by increasing the activity of methylmalonyl-coenzyme A (CoA) mutase, a vitamin B_{12}-dependent enzyme and important component of the Krebs or tricarboxylic acid (TCA) cycle (Kennedy *et al*., 1990) [41]. Butaphosphan, an organic phosphorus source, has been also been used because of its presumed role in gluconeogenesis (Rollin *et al*., 2010) [61].

Treatment of ketotic animals with 300 g of propylene glycol daily should be considered the base of ketosis treatment. It is generally given as an oral drench once a day. When propylene glycol enters the rumen, it is either absorbed directly or converted to propionate (Nielsen and Ingvartsen, 2004) [56]. Propylene glycol that is absorbed directly enters the TCA cycle to increase oxidation of acetyl CoA and stimulate gluconeogenesis. Propionate from propylene glycol can also be used for gluconeogenesis and helps stimulate insulin release. There is a significant increase in insulin by 15 minutes after administration, and insulin remains increased for 2 hours or more after drenching. This spike in insulin helps decrease fat breakdown and hepatic ketone body production (Studer *et al*., 1993) [71].

Prevention and control

Fattening of animals during pregnancy must be avoided and the score should be maintain between 3.5 and 4.0 on 5 point scale. The pregnant animal should be kapt on balanced diet and concentrate more than 1 kg/50 kg b.wt. should not be given. The ration should have a minimum of 20% crude fibre along with supplementation of essential vitamins and minerals. Monensin is known to reduce ketosis in herd as it alters the ratio of volatile fatty acids produced by rumen fermentation. (Sauer *et al*., 1989) [62].

Downer cow syndrome

The condition, which most frequently manifests in the first two or three days following calving in high-producing dairy cows immediately after milk fever, is clinically recognized by persistent recumbency even after two successive calcium treatments. Following treatment for milk fever, cows who do not fully recover and stand but instead remain recumbent frequently develop ischemic necrosis of the major muscles of the pelvic limbs, injuries to the tissues around the hip joint, and lesions to the obturator muscles. The majority of the time, alert downer cows are in a recumbent position as a result of musculoskeletal or neurological injuries, such as lesions of the sciatic or obturator nerve brought on by dystocia (calving paralysis), long bone or pelvic fractures, hip luxation, or muscle damage brought on by either primary trauma or prolonged recumbency. Cows that are unsteady during parturition or who are made to stand or walk on a slick floor right before or after parturition are also more likely to sustain injuries to their musculoskeletal system. The other cause is electrolyte imbalance brought on by prolonged recumbency after delivery, such as hypophosphataemia, hypokalaemia, and hypomagnesaemia.

Clinical findings

The vast majority of the affected animals are awake and aware, ruminating, pooping, and urination normally. They try to get up with their forelimbs, but they are unsuccessful. These cows are known as creeper cows (Sharma *et al*., 2009) [65]. The cow's hind limbs may often stretch to the elbows on each side of the cow. The medial thigh muscles of the cow are under a great deal of pressure in this position, which can lead to ischemic necrosis, coliform mastitis, decubitus ulceration, particularly over the prominences of the hock and elbow joint, and traumatic injuries around the tuber coxae brought on by the hip slings. After 7 days, the prognosis for the reclining animals is bleak, and the majority of them pass away from myocarditis.

Diagnosis

The blood levels of calcium, phosphorus, magnesium, and glucose are all within the normal range, and the outcomes of

haematological tests typically match those of healthy cows that have recently given birth. By 18 to 24 hours after the commencement of recumbency, the levels of the enzymes creatine phosphokinase (CPK) and aspartate aminotransferase (AST) are typically noticeably raised and continue to rise during the following few days. CPK levels that keep rising are a sign of ongoing muscle injury. By 18 to 24 hours after the commencement of recumbency, a significant proteinuria is typically detectable.

Line of treatment

Along with medical management, a Downer cow's good nursing care and management are priorities. Good bedding, especially enough straw or a soft ground surface, is helpful in healing. When downer cows try to stand, the best ground surface for them to stand on is a sand or mud pack. Frequent side-to-side rolling of the affected animal is important to reduce ischemia necrosis. Supplementing with a composite solution combining calcium, magnesium, phosphorus, and electrolyte solution is a part of therapeutic management. Early healing is aided by the use of nervine tonics such vitamin B complex.

Prevention and control

The incidence and severity of downer cow syndrome will be decreased by the early diagnosis and treatment of milk fever. Every few hours, if they are unable to stand, they should be turned from side to side. Prior to calving, dairy cows should be kept in a cosy, well-bedded box stall, and if milk fever occurs, they should remain there for at least 48 hours after partition.

Conclusion

The dairy business continues to face a significant threat from metabolic illness. For dairy farmers, metabolic illness is a significant source of financial loss. Systems for managing the health and performance of dairy cows are centred on the early detection and subsequent avoidance of production disorders through the treatment of afflicted animals or by enhancing the diet of the herd. Avoid overfeeding the animals and making sudden changes to their feeding plan. Give the animals the appropriate amounts of protein, vitamins, and minerals, as well as adequate amounts of high-quality roughage.

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