Review Article

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OXIDATIVE STRESS INDICATORS DURING PERIPARTUM UTERINE INFECTION OF BUFFALOES: A REVIEW

Prachurya Biswal[1,*], Surender Singh Lathwal[2], Rubina Kumari Baithalu[2] and Deepanker Bisht[3]

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ABSTRACT

The transition of dairy animals from the period of pregnancy to next lactation considerably enhances the need for source of carbohydrates, proteins, lipids and other nutrients for various metabolic activities. At the same time, the dry matter intake is generally decreased resulting to negative energy balance ultimately compromising the immunity, which leads to oxidative stress as a result of enhanced free radicals in body and makes the animal vulnerable to metabolic as well as infectious diseases. Diseases related to reproductive system especially uterine infections *viz*. endometritis, metritis during the peri partum period is the most widespread reason of infertility in dairy sector leading to enhancing the interval for uterine involution, occurrence of first oestrus, number of services/ conception and service period. The adverse effects on fertility of animal, health status and the treatment cost prove that uterine infections are considered as one of the most serious and expensive conditions, challenging the buffalo sector. Hence, current researchers aim to find some indicator molecules which will predict the diseases before their onset so that by managemental and nutritional interventions it can be minimised, further animal will suffer less, and better management and welfare will be achieved. The objective of this review article is to discuss about the occurrence of oxidative stress during peripartum period and the physical status of Murrah buffaloes during the said period by assessing the Nitric oxide (NO), Malondialdehyde (MDA) and Total antioxidant capacity (TAC) status.

Keywords: *Bubalus bubalis*, buffaloes, oxidative stress, uterine infections, oxidative stress indicator

INTRODUCTION

Buffaloes mostly found in the Indian subcontinent *viz*. Murrah, *Nili Ravi*, Jaffrabadi, Mehsana, Surti etc. are considered to have the major role in milk tank of India. Their contribution is around 55% in India's milk tank whereas the contribution in Asia and world is around 38% and 12.1% respectively (FAO STAT, 2007). The Peripartum duration which is extended from -21 days to + 21 days of parturition is the gravest

[1]Department of Livestock Production Management, College of Veterinary and Animal Sciences, Bihar, India, *E-mail: prachuryabiswalvet@gmail.com
[2]Indian Council of Agricultural Research, National Dairy Research Institute, Haryana, India
[3]Department of Biochemistry, Khalsa College of Veterinary and Animal Sciences, Punjab, India

time for dairy animals as they have to combat the physical, physiological, hormonal, environmental stress resulting into compromised immune response, resulting into various infections related to reproductive system (Smith and Risco, 2005). According to reports the yearly occurrence of uterine infections in dairy buffalo farms during the postpartum period is 20 to 75% (Usmani *et al*., 2001). Production of reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) during this period plays a significant role in damage to macromolecules and leads to oxidative stress, compromising the immune status and making the animals vulnerable to various infectious diseases (Sordillo, 2005; Wilde, 2006).

Diminished antioxidant status, lower conc. of ascorbic acid as well as glutathione conc. are believed to be highly correlated with many peripartum diseases *viz*. mastitis, subclinical and clinical endometritis (Hanafi *et al*., 2008; Heidarpour *et al*., 2012). As a part of immune response, phagocytes produce considerable amount of Nitric oxide (NO) and myeloperoxidase enzyme during the inflammation process in case of uterine infections and mastitis. They together constitute a compound nitrotyrosine, which results in disintegration of protein structures and have a negative effect on cell stability (Jozwik *et al*., 2012). It is a fact that oxidative stress generated by enhanced ROS cause damage to the lipids by lipid peroxidation and by estimating MDA, we can quantify lipid peroxidation (Nielsen *et al*., 1997). According to a study lower conc. of serum TAC, higher conc. of lipid peroxidation and Nitric Oxide were produced during the peripartum window leads to the onset of oxidative stress, additionally, negotiate the overall health status especially the uterine health during postpartum stage which may last lifelong in dairy cattle and buffaloes (Baithalu *et al*., 2016; Biswal *et al*., 2020). Oxidative stress indicators have been presented as prognostic and diagnostic indicators for many animal diseases. Assessment of these molecules during peripartum period buffaloes has not been explored much. Therefore, the current review targets to emphasize potentials of oxidative and antioxidative biomolecules as diagnostic indicators of uterine diseases in buffaloes.

MATERIALS AND METHODS

Peripartum window - threat to dairy animals

The peripartum period for dairy animals usually extends from 3 weeks before parturition to 3 weeks after parturition (Grummer, 1995; Smith and Risco, 2005; Contreras and Sordillo, 2011), also known as the most crucial period of a dairy animal. This peripartum period is believed to give rise a higher occurrence of various diseases impairing the health, production in dairy animals (Drackley, 1999). During both prepartum and postpartum stage dairy animals need more energy supplement than they are able to consume and during this period dry mater intake (DMI) approximately reduced to 30% resulting in the Negative Energy Balance (NEB) (Bell, 1995; Sundrum, 2015). Consequences of this NEB cause lipolysis, increase in the conc. of non-esterified fatty acids (NEFA) and β-Hydroxybutyrate (BHBA) (Drackley *et al*., 2005; Melendez *et al*., 2004; Sundrum, 2015). As a result of this dairy animals start mobilizing their body materials to fulfil their enhanced energy requirements for milk production, maintenance and mainly use lipids as energy sources (Contreras and Sordillo, 2011; Wathes *et al*., 2007). The increased lipid mobilization disrupts various inflammatory and immune reactions of body and supports generation of free radicals by leukocytes and endothelial cells (Lacetera *et al*., 2004; Scalia *et al*., 2006; Contreras and Sordillo, 2011; Valko *et al*., 2007; Schonfeld and Wojtczak, 2008). Studies reported that there is increased generation of ROS and RNS during this peripartum window (Rizzo *et al*., 2012) which damages various macro molecules like proteins, lipids, DNA (Trevisan *et al*., 2001) and results in oxidative stress. This contributes to deviation of physiological functions and results health glitches in dairy animals (Ranjan *et al*., 2005; Lykkesfeldt and Svendsen, 2007; Zhao and Lacasse, 2008; Salman *et al*., 2009). Further research is required in case of buffaloes for clearer picture of peripartum oxidative stress in relation to physiological changes and postpartum animal health.

Oxidative stress during peripartum period

Oxidative stress occurs when ROS are present in abundance as compared to enzymatic and non-enzymatic antioxidants. It stimulates dysfunction of inflammatory response in dairy animals during periparturient stage (Sordillo and Aitken, 2009). In normal metabolic process ROS are generated generally as the product of mitochondrial respiratory pathway by the initiation of NADPH oxidase (Sordillo and Aitken, 2009). When the NADPH oxidase ignites the phagocytic cells for phagocytosis of pathogens, there is generation of superoxide anions and hydrogen peroxide, also known as oxidative burst (Valko *et al*., 2007). In dairy animals oxidative stress during peripartum period is corelated with lipid peroxidation significantly (Castillo *et al*., 2006). The main reasons for the physiological and metabolic stress in dairy animals are considered to be transition of non-secretory parenchyma to secretory parenchyma in udder, rapid mammary gland growth and development, high energy requirement, oxidative stress (Gitto *et al*., 2002). The natural antioxidant defence mechanism of body i.e. enzyme mechanisms regulated by superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase and non-enzyme mechanisms regulated by vitamin E and selenium (Sharma *et al*., 2011) which mainly regulate the free radicals generated in the body. Generation of free radicals and ROS than the amount neutralized weakens the immune mechanism of body, leading to damage of macro molecules and pathway of metabolic reactions (Trevisan *et al*., 2001; Joksimovik-Todorovic and Davidovic, 2007).

It implies that amounts of superoxide anions and hydrogen peroxide ions that are produced as a result of general metabolic activities gives rise to oxidative stress in dairy animals when the systemic antioxidant mechanism fails to neutralise it. In case of buffaloes the aspect of minimising oxidative stress by nutritional interventions needs to be explored much as it is directly related to production and animal welfare.

Compromised immunity during peripartum period

According to studies, it is an established fact that, there is a positive correlation among stress and disease susceptibility in case of dairy animals. Existing reports suggest that the hormone glucocorticoid weakens the immune system and stimulates the hypothalamic pituitary adreno cortical (HPA) axis (Griffin, 1974). Symptoms of weaken immune system during last trimester of pregnancy are associated with the inflammatory response and oxidative stress conditions in early lactation period (Kehrli *et al*., 1989; Lacetera *et al*., 2005; Sander *et al*., 2011). The weakened immune system makes the dairy animals vulnerable to mastitis and other infectious ailments related to reproductive system. This impaired defence system results in metabolic stress which is the consequences of higher milk yield and reduced nutrients uptake (Pond & Newsholme, 1999). Another possibility is that multiple stressors can deviate resources for the metabolic system like energy, amino acids, etc. and results in immune suppression (Drackley *et al*., 2005). Several physiological alterations such as metabolic diseases and changes in concentration of steroid hormones (glucocorticoids, oestradiol, and progesterone) play a crucial role in suppressed immunity (Waldron and Revelo, 2008).

Dairy animals are more susceptible to oxidative stress caused by imbalance of free radicals and low antioxidant capacity during the advanced parturition stage as compared to the early lactation stage, which contribute to the occurrence of numerous metabolic ailments and uterine diseases (Ellah *et al*., 2016; Bernabucci *et al*., 2005; Castillo *et al*., 2005, 2006; Sordillo and Aitken, 2009). Decreased phagocytic activity and intracellular killing by neutrophils and circulating vitamin A, E (α-tocopherol) and selenium concentration around calving is a cause of compromised immunity (Hogan *et al*., 1992). Many researchers have reported that the antioxidant capacity during the peripartum window of dairy animals is not capable to neutralise the free radicals generated due to increased ROS supply (Bernabucci *et al*., 2005; Castillo *et al*., 2005). The ultimate effect of uterine infection is to damage the uterine endometrium and causing inflammation with initiation of proinflammatory cytokines, including tumour necrosis factor- α (TNFα), interleukin-1 (IL-1), and interleukin-6 (IL-6), and chemokines, including interleukin-8 (IL-8) (Chapwanya *et al*., 2009; Galvao *et al*., 2011). Baithalu *et al*., 2016 has reported that there was impaired movement and diminished phagocytic activity of neutrophils in dairy animals that had given rise to uterine infection. It was another possible reason for failure of eliminating the pathogens from uterine lumen leading to uterine diseases in dairy animals. She further reported, there was less conc. of oestradiol and higher conc. of cortisol in peripheral circulation of cows resulting in uterine infection.

From the above findings it can be suggested that compromised immunity during peripartum period is due to change in hormonal scenario, oxidative stress making animals vulnerable to various diseases. Further it may be concluded that peripartum is the most crucial stage in animal which requires the most attention. Hence, it has been suggested to improve feed intake of buffaloes during peripartum period as well as providing supplements and additives containing vitamin E, selenium, choline etc. so that extent of oxidative stress will be minimised, and occurrence of postpartum diseases will be reduced.

Postpartum infectious diseases in dairy animals

The challenge for reproductive biologists is to understand the mechanisms of bacterial interventions in uterine tissue and the related consequences like weakened immunity on the reproductive system and reproductive efficacy of bovines (Sheldon and Dobson, 2003). Uterine lumen is generally sterile before calving and if any type of bacterial attack onsets, there is resorption of foetus or abortion in maximum cases (Semambo *et al*., 1991). Postpartum uterine contaminations suppress the fertility of dairy animals by delaying the uterine involution period as well as time to onset of first cyclicity and estrus and increase the no of services per conception (Fourichon *et al*., 2000; Gilbert *et al*., 2005; McDougall, 2007; Galvao *et al*., 2009). The bacterial infection in uterine tissue is non-specific in nature and includes a broad range of bacterial species (Griffin *et al*., 1974; Sheldon *et al*., 2002). On the other hand, the phagocytic activity of neutrophils is diminished after parturition in many dairy animals, and this influences the onset of infections in uterus (Zerbe *et al*., 2000). Immune cells are designed to sense antigens such as bacterial endotoxin and peptidoglycan through toll-like receptors, which initiates a down-stream signalling pathway to arouse the production of cytokines i.e. chemical messengers including tumour necrosis factor-alpha (TNF-α), and interleukins (IL-1, IL-6, IL-8) (Beutler *et al*., 2003).

Another factor that makes the dairy animals more vulnerable to periparturient infectious diseases may be the marked decrease in PMN chemiluminescence and viability in milk PMN of pluriparous animals. The diminished phagocytic activity and immunocompromising around parturition may be due to more band cell production with no component to fight with the infection (Meglia *et al*., 2001; Dang *et al*., 2012). The prominent uterine bacteria most often associated with clinical disease are *Arcanobacterium pyogenes, Escherichia coli, Fusobacterium necrophorum* and *Prevotella melaninogenicus* (Sheldon *et al*., 2002). *A. pyogenes, F. necrophorum* and *P. melaninogenicus* act additively to advance the ruggedness of uterine diseases (Griffin *et al*., 1974; Ruder *et al*., 1981; Olson *et al*., 1984; Bonnett *et al*., 1991). Pyometra is established by premature ovulation following calving and commencement of progesterone stage before obliteration of bacterial intervention in uterus (Olson *et al*., 1984). Metritis, a harsh inflammatory reaction which involves all the layers of the womb: endometrium, submucosa, muscularis and serosa (BonDurant, 1999) whereas, the superficial inflammation of the endometrium extending up to the stratum spongiosum is known as Endometritis (BonDurant, 1999). Presence of pus in vagina on 21 days or more during postpartum clinically symbolises endometritis and often associated with postponed uterine involution (Sheldon and Noakes, 1998). Incidence of uterine infection can be reduced to some extent by administration of vitamin E and Se in cows (Singh, 2017). However reproductive parameters such as commencement of first postpartum estrous, onset of first cyclicity, service period was improved in cows treated with vitamin E and Se (Singh, 2017). However, this aspect is not explored much in case of buffaloes which act as the culprit for compromised immunity and infertility. More studies should be encouraged with nutritional and managemental manipulation as well as peripartum changes in buffaloes to combat uterine infections.

RESULTS AND DISCUSSIONS

Oxidative stress indicators

Nitric Oxide (NO) free radical

NO is a common free radical having a single electron and is highly reactive as half-life is very short about 2 to 6 seconds. It is mainly produced during inflammatory conditions (Moilanen and Vapaatalo, 1995; Mac Micking *et al*., 1997) by phagocytes as a part of immune reaction and acts as cytotoxic mediator when it is released in excessive amounts during *E. coli* infection. In animals suffering from mastitis, neutrophils in their system produce considerable amount of NO and the myeloperoxidase enzyme, i.e. substances that combinedly may lead to the formation of nitro tyrosine, which has the ability to degenerate proteins and have a destructive effect on tissues (Jozwik *et al*., 2012). Blum *et al*.

(2000) has suggested that a positive correlation present between intramammary and systemic TNF-α and NO generation in acute mastitis. NO has antibacterial properties due to peroxynitrite (reactive nitrogen metabolite) derived from oxidation of nitric oxide (Beckman *et al*., 1990) and regarded as a primary defence system (Huie and Padmaja, 1993; Okamoto *et al*., 1997). Higher levels of peripheral NO were correlated with uterine infections in cattle and buffaloes during postpartum stage (Li *et al*., 2010; Mili and Pandita (2014). In cows that developed uterine infection had shown elevated concentration of NO in peripheral circulation during one-week prepartum to the day of parturition than cows that did not develop uterine infections has been suggested by Baithalu *et al*. (2016).

Malondialdehyde (MDA)

Malondialdehyde is estimated as an indicator of oxidative stress and it is produced as consequences of lipid peroxidation. It is a reactive carbonyl compound and shows damaging effect on cells in higher amount by altering their function either by reacting with DNA to form DNA adducts or by damaging the cellular protein (Marnett, 1999). Quantification of MDA in biological fluids in done by using several methodologies, one of them is measuring the thiobarbituric acid reactive substances (TBARS) (Janero, 1990), which is the most used method (Bernabucci *et al*., 2002, 2005; Gabai *et al*., 2004; Wullepit *et al*., 2009, 2012; Tanaka *et al*., 2011). Higher peripheral concentration of MDA during one week before calving to one week after calving and the highest level on the day of calving in cows that developed uterine infection than cows that did not develop uterine infections has been reported by Baithalu *et al*. (2016).

Total antioxidant capacity (TAC)

During the peripartum window oxidative stress is a considerable factor in weakening of the immune system which amplify the sensitivity of individual animals to different health hazards (Sordillo, 2005; Wilde, 2006). According to the reports of many studies the plasma concentration of trace minerals and vitamins mainly vitamin E (α-tocopherol), Se, Cu and Zn can reduce noticeably in dairy cows during peripartum phase (Goff and Stable, 1990; Weiss *et al*., 1997, Politis *et al*., 1995; Meglia *et al*., 2001). Monem and El-Shahat (2011) has reported that dietary deficiencies of minerals and vitamins are generally observed in ruminants. Low conc. of plasma antioxidant status, TAC, ascorbic acid and diminished glutathione conc. are associated with mastitis, sub clinical and clinical endometritis has been demonstrated by many studies (Hanafi *et al*., 2008; Heidarpour *et al*., 2012). Measuring antioxidant capacity evaluates the combined action of all the antioxidants present in plasma and body fluids, thus providing an integrated parameter for measuring antioxidants (Ghiselli *et al*., 2001). Total antioxidant capacity as a single measure may effectively describe the dynamic equilibrium between pro-oxidants and antioxidant in the plasma constituent (Cao and Prior, 1998; Ghiselli *et al*., 2001). By measuring the TAC in plasma, the antioxidant status of an animal body can be measured, which is the outcome of interaction of many different compounds and systemic metabolic interactions (Ghiselli *et al*., 2001).

NO, tac and mda: Indicators of peripartum diseases

Oxidative stress is considered as the key factor causing compromization of the immune system of the animals impairing the response to inflammatory conditions which leads to numerous health problems in dairy animals (Ibrahim, 2015). Observations shows that all indicators of the antioxidant defence system were higher in buffalo than in bovine cows, while the indicators of the oxidative modifications were higher in bovine than in buffalo cows (Cigliano *et al*., 2014). Serum TAS (total antioxidant status) values were significantly reduced in all diseased animals whereas MDA (malondialdehyde) concentrations were dramatically enhanced in animals with clinical endometritis. Hence, the function of antioxidant system is probably significant to the establishment and persistence of endometritis (Bliznetsova *et al*., 2008; Hanafi *et al*., 2008). Heidarpour *et al*. (2012) suggested that cows and buffalos suffering from endometritis have decline in serum TAS values may be due to over utilization or sequestration of antioxidants to neutralize the over production of ROS during inflammatory process of the uterus. Considerably enhanced peripheral concentration of NO, MDA during peripartum stage make dairy animals more vulnerable to postpartum uterine infection (Baithalu *et al*., 2016). MDA or TBARS concentration is enhanced around calving in dairy animals (Bernabucci *et al*., 2002, 2005; Bouwstra *et al*., 2008). Nisbet *et al.* (2007) has suggested that enhancement in NO concentration in diseased cattle was a result of promotion of NO synthesis in macrophages by bacterial lipopolysaccharides and can be used as an indicator of tissue damage. Piccinni *et al.* (2004) concluded that during pregnancy, NO concentration in plasma gradually declined from the precalving to the postcalving period, with enhanced concentration during first two weeks after calving than the following weeks. The enhanced concentration of NO was observed in blood plasma during gestation as compared to non-pregnant buffaloes. The increased levels of plasma nitric oxide continue till the day of parturition, whereas the concentration started declining on day 3rd postpartum. Increased peripheral level of MDA and NO during one week before parturition to one week after parturition and the highest level on the day of calving in cows that developed uterine infection than cows that did not develop uterine infections have been reported by Baithalu *et al.* (2016).

From the above discussions it can be suggested that NO, MDA and TAC can be used as indicators of oxidative stress and upcoming uterine infection in buffaloes which will help in prediction of disease before their clinical onset. However, literature in this scenario is very limited, hence more research should be conducted for identification of oxidative stress indicators in buffaloes to use them as diagnostic prognostic purpose.

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