Review
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THE IMPACT OF OXIDATIVE STRESS ON REPRODUCTIVE DISORDERS IN COWS – A REVIEW

Horațiu RAFA[1], Monica Irina NAN[1], Sanda ANDREI[1*]

[1] Department of Preclinical Sciences, Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine, Cluj-Napoca, Romania

e-mail: sandrei@usamvcluj.ro

Abstract

During the transition period dairy cattle are more susceptible to disease because many aspects of the immune system are altered by uncontrolled inflammation, a condition that has as a cause the metabolic adaptation of the cows. Inflammation and oxidative stress are interlinked, and contribute to the evolution of reproduction diseases of dairy cows. Our review highlights to light scientific data on oxidative stress and reproductive disorders in dairy cows. The information collected is significant for animal welfare and reproduction, and it will create the foundation for future research on the connection between oxidative stress, reproductive diseases, and nutrition in cows.

Key words: c**ows, oxidative stress, reproductive disorders**

INTRODUCTION

Since dairy cows use large reserves of glucose for the synthesis of lactose in milk during the approximately six-week transition period - three weeks prior to and three weeks following calving it is important to understand the relationship between oxidative stress and reproduction diseases in these animals. Ruminants can produce glucose through a process called gluconeogenesis. Propionic acid is one resource that is utilized in the production of glucose. Adipocytes release non-esterified fatty acids (NEFAs) through lipolysis, which is caused by a decrease in the secretion of insulin as a result of low blood glucose levels (Herdt, 2000).

Hypoglycemia lowers energy levels and milk production. Ketones are another type of metabolite that enter the bloodstream as a result of the liver's metabolism of fatty acids. The β-hydroxybutyrate (BHB) is the most prevalent ketonic body and can be used to assess the body's spectrum of lipid mobilization as well as negative energy balance (NEB) (Sordillo and Raphael, 2013).

Oxidative stress is caused by the generation and excessive accumulation of reactive oxygen species (ROS) as a result of an imbalance in the prooxidants/antioxidants ratio in favor of prooxidants. Many pathological conditions, including degenerative diseases, cardiovascular diseases, immuno-inflammatory lesions, nervous system disorders, diabetes, thyroid disorders, gastric ulcers, and even viral infections, are linked to the state of oxidative stress as a cause in both their initial development and progression. From an experimental point of view, increased concentrations of products that result from the oxidative degradation of biomolecules, lipids and lipid components, amino acids and proteins, and nucleic acids can be observed in the state of oxidative stress (Andrei et al., 2014).

Lipid mobilization and oxidative stress during the transition period

Studies of Valko et al. (2007) and Contreras et al. (2010) provide evidence in favor of the theory that a high level of lipid mobilization promotes infectious disorders including mastitis and metritis. One of the primary causes for the immune system's decreased antibacterial activity during the start of lactation is lipid metabolism (Kimura et al., 1999). Because β-hydroxybutyrate affects leukocyte and neutrophil activity, ketosis increases the risk of mastitis and other infections in cows (Sordillo and Raphael, 2013).

Neutrophils and macrophages are negatively impacted by decreased glucose concentration caused by NEB since they require glucose to maintain their antimicrobial activity (Suriyasathaporn et al., 2000; Calder et al., 2007; Sordillo and Raphael, 2013). O'Boyle et al. (2012) state that blood glucose concentration decreases during intense lipid mobilization may restrict the amount of energy required for immune cell populations to function appropriately intended.

Other production-related processes, including milk synthesis and secretion, may compete with an active inflammatory response for limited nutrients (Plank and Hill, 2000). One possible explanation for the decreased milk production of dairy cows during diseases could be the competition for an insufficient supply of glucose. Additionally, because BHB inhibits leukocyte antimicrobial activity, hyperketonemia might negatively impact a number of critical immunological systems and make transition cows more susceptible to disease (Suriyasathaporn et al. 2000).

To assess the impact of milk production and NEB on various immune parameters pregnant dairy cows were mastectomised while maintaining the endocrine changes associated with late pregnancy and parturition (Kimura et al. 1999; Kimura et al. 2002; Nonnecke et al. 2003). The mastectomised cows showed extremely low increases in NEFA during the periparturient phase in comparison to the cows with intact mammary glands. Even while immune function in cows that had their mastectomies was temporarily reduced around calving, lymphocyte and neutrophil functions were significantly diminished in cows that had their mammary glands eliminated (Kimura et al., 1999; Nonnecke et al., 2003). Additional study has shown that parturition itself, and the resulting alterations in steroid hormone levels, is not the primary immunosuppressive component in periparturient cows. According to Sordillo and Mavangira (2014), the detrimental effect on immune cell populations was most likely caused by the higher metabolic needs of early lactation.

The composition and concentration of free fatty acids in the plasma changes during lipid mobilization, which is important for immune cell activity and particularly for their structure. Thus, palmitic acid, stearic acid, and oleic acid constitute the majority of free fatty acids during parturition. On the other hand, there is a decrease in the amount of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). During parturition, the profile of free fatty acids may impact the cow's proinflammatory response (Douglas et al. 2007; Contreras et al. 2010; Sordillo and Raphael, 2013).

Free fatty acids modulate the inflammatory response by influencing the synthesis of eicosanoids, lipid mediators. Leukotrienes, prostaglandins, thromboxanes, resolvins, lipoxins, and proteins are examples of eicosanoids, which are largely produced by macrophages and endothelial cells. The phospholipids that compose the membranes of cells are the source of eicosanoids, which are produced from omega-3 and omega-6 polyunsaturated fatty acids. ADH and AEP are examples of the omega-3 acids that are involved in the synthesis of eicosanoids. Linoleic acid and arachidonic acid are examples of omega-6 acids. These fatty acids are substrates for lipoxygenases or cyclooxygenases that oxidize substrates enzymatically. While eicosanoids derived from omega-3 acids reduce inflammation, those derived from omega-6 acids increase the inflammatory response (Douglas et al. 2007; Serhan, 2009; Contreras et al. 2010; Sordillo and Raphael, 2013).

Inflammation and oxidative stress interact in order to produce chronic inflammation. Through the activity of reactive oxygen species (ROS), which activate nuclear factor kB and stimulate the expression of mediating lipids, oxidative stress affects the pathways of the proinflammatory response. Oxidative stress is made exacerbated by the accumulation of excess ROS in the mitochondria as a result of TNF-α exposure to endothelial cells and macrophages (Sordillo and Raphael, 2013).

Cows with moderate to severe fatty livers showed higher blood amounts of TNF-α, according to Ohtsuka et al. (2001). During the first week of lactation and the late stages of lactation, TNF-κ administrations to cows induced insulin resistance, higher liver levels of triglycerides, and elevated inflammatory markers, all of which negatively impacted the cows' health and the production of milk (Yuan et al. 2013; Sordillo and Mavangira, 2014).

Proinflammatory molecules, nitric oxide, cytokines and eicosanoids are released during inflammation, courtesy to local immune and non-immune cells of the affected tissue, which recognize pathogens through receptors (Sordillo and Raphael, 2013). The local endothelium is affected by these inflammatory mediators, which increase blood volume and facilitate leukocyte migration to the infection site. Acute phase proteins are released from the liver, tachycardia, reduced appetite, and hyperthermia are further symptoms of a systemic inflammatory response that can be caused by cytokines and eicosanoids. The invasive infections are eliminated after the inflammatory reaction, the immune system returns to normal, and the tissues recover their typical morphology and function (Sordillo and Raphael, 2013).

A large amount of additional information indicates that an increase in infectious and metabolic disorders during the period of transition is an indicators of oxidative stress, modified energy metabolism, and impaired host defenses (Sordillo et al., 2009, Sordillo and Raphael, 2013, Sordillo and Mavangira, 2014)

Oxidative stress and reproductive disorders

Follicular cyst

When a mature follicle doesn't ovulation and continues to mature for 10 days or more, it can develop into a cyst. There are two types of cysts: luteinized and follicular cysts. Low levels of progesterone and a thin wall are characteristics of follicular cysts. Thick walls and elevated levels of progesterone are two characteristics of luteinized cysts (Douthwaite and Dobson, 2000).

Nutritional deficits are the main factor causing ovarian follicular cyst formation in the early postpartum period. Ovarian follicular cyst incidence is associated with the length and/or severity of the negative energy balance (Vanholder et al., 2006).

The ROS level dropped between 36 and 84 hours after PGF2a was given to a cow with a cystic ovary. Conversely, cows with cysts had higher levels of antioxidants than other cows with regular ovulation. The physiological processes that lead to ovulation could have been disturbed by the imbalance between oxidants and antioxidants, which promotes the development of ovarian cysts (Talukder et al., 2014).

According to Brodzki et al. (2019), cows with luteal cysts displayed higher levels of TNF-α and IL-6 than cows with other ovarian structures. Moreover, cows with multiple types of ovarian cysts have been shown to have elevated levels of IL-10. Additionally, both forms of cysts in cows were associated with high levels of acute phase proteins, haptoglobin [Hp] and serum amyloid A [SAA]; however, the concentrations of both proteins were higher in cows with follicular cysts. Inhibiting the local inflammatory response and preventing an autoimmune reaction to the tissues is an essential function of the anti-inflammatory cytokine IL-10. Leukocyte passage into the ovarian follicle, proinflammatory cytokines, chemokines, and enzymes actively involved in ovulation are released during the preovulatory period since ovulation is considered as an inflammatory event. IL-10 levels at that point may have an impact on immunosuppressive activity and ovulation suppression.

Metritis

An infection called metritis can develop in a cow's uterus during the postpartum period. Typically, this is a gram-negative anaerobic bacterial infection caused on by bacteria that entered the uterus via iatrogenic means or colonized the vagina. It has been demonstrated that immunosuppression during the postpartum period, starting 1-2 weeks before to calving, predisposes cows to metritis. Metritis was shown to be 2.58 and 4.32 times more prevalent in cows with dystocia than in animals who had a normal calving. A possible approach in order to counteract this prepartum immunosuppression is modifying the duodenum's omega-6: omega-3 fatty acid ratio. It appears that the functional properties of mononuclear cells can be enhanced in multiparous cows before calving by raising the n-6 : n-3 ratio. Research has indicated that consuming a diet high in omega-3 to omega-6 fatty acids (15:1) or more, may improve reproductive health during the period of lactation (Cargile and Tracy, 2015).

In relation to the development of postpartum uterine infections in zebu cows, Baithalu et al. (2016) noticed changes in peripheral concentrations of total antioxidant capacity (TAC), malondialdehyde (MDA), and nitric oxide in association with the endometrial expression of genes encoding antioxidant enzymes. In the peripartum period, low serum TAC and high levels of MDA and nitric oxide can affect the expression of antioxidant genes in the endometrium, compromising uterine health and leading to the development of postpartum puerperal metritis and clinical endometritis in cows. Consequently, postpartum uterine infection in cows can occur due to the elevated level of oxidative stress during the prepartum and postpartum periods as well as immediately after calving.

According to a study by Kizil et al. (2010), there was a decrease in glutathione peroxidase (GPx) and catalase (CAT) activity simultaneously with an increase in plasma MDA concentration in cows with puerperal metritis compared to the control group. The amplification of oxidative stress during metritis was confirmed by the rise in MDA concentrations and the suppression of antioxidant enzyme activity. The group of cows with puerperal metritis exhibited significantly lower plasma concentrations of vitamin A, E, C, and β-carotene on an individual level compared with the control group.

Postpartum hypocalcemia

Clinical or subclinical hypocalcemia in cows during the periparturient period increases the incidence of secondary diseases like metritis, dystocia, uterine prolapse, and placental retention. Hypocalcemia can result from a number of factors, including as insufficient calcium in the prepartum diet, high dietary phosphorus levels, low magnesium levels, and older age. Fatigue, cold extremities, and a weak, quick pulse are the most typical symptoms of milk fever that are seen during stage 2 of calving. It is thought that the

pathognomonic diagnosis of hypocalcemia in cattle is serum total calcium of less than 8.0 mg/dL. Reducing the amount of calcium consumed prior to calving so that the animal's total daily absorption of calcium is less than 20 g is the conventional strategy for reducing the frequency of hypocalcemia. As a result, more calcium is reabsorbed from the bone and the production of bovine parathyroid hormone is stimulated (Cargile and Tracy, 2015).

Research indicates that some feed management strategies, such as the differentiated cation-anion diet (DCAD), which includes negatively charged anionic minerals in the diet of the cows, can be used to reduce the risks associated with calving. Calcium induces a hormonal response in the postpartum period, preventing calcium insufficiency and preparing the animal for a high demand for calcium during this time. The ideal time to employ anionic diets is 21 days prior to calving, as this leads to a permanent mobilization of calcium regulating systems and prevent hypocalcemia (Albani et al., 2017).

Meyer and Harvey (2004) suggest that during calving, oxidative stress occurs in cells due to high muscle effort and high calcium demand, making the animal more vulnerable to disorder such as hypocalcemia, placental retention, and postpartum metritis.

Dairy cows who receive an anionic diet prior to calving experience positive health effects. This diet generally lowers the generation of free radicals, lowers lipid peroxidation during the postpartum period, and avoids subclinical hypocalcemia. The constant increase in sulfur and chlorine concentrations, as well as the decrease in potassium and sodium levels during the last three weeks of gestation, are evidence of the effects of anionic diets, which may significantly reduce hypocalcemia in cows. The DCAD diet, which results in a slower decrease in calcium and a faster mobilization of it, is the source of the appearance of a faster calcium homeostasis (Peacock, 2010). The total levels of protein, albumin, globulin, cholesterol, triglycerides, urea, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and gamma-glutamyl-transferase (GGT) were not significantly affected by the anionic diet. However, during the transition period, the majority of these variables exhibited modifications. These modifications occurred because the body needs a lot of nutrients at this precise moment in order to produce colostrum and milk (Albani et al., 2017).

Fetal membrane retention

The main cause of fetal membrane retention is the fetal cotyledon's villi failing to separate from the mother crypts of the caruncle. The process of separation ends approximately eight hours post calving, depending on the animal's age and parity. In general, between 0.5–12 hours after calving, all components of the allantochorion and amniosis should be removed (Peter, 2015).

Placental retention can be caused by a number of conditions, including dystocia, malnutrition, higher parity, and hormonal defects. Furthermore, a lack of certain vitamins and minerals may result in placental retention. The deficiency of microelements and the negative energy balance indicate synergism regarding the oxidative stress during the prepartum phase. In addition, the increased metabolic requirements of late pregnancy, calving, and lactation may exacerbate the generation and the accumulation of ROS (Elsayed et al., 2020).

The naturally detached and retained placenta exhibited altered antioxidant enzyme activity shortly after parturition, particularly for the enzymes GPx, superoxide dismutase (SOD), glutathione transferase (GSH-Tr), and catalase (CAT), Additionally, lipid peroxidation was shown to be higher in the placental tissues of cows with retained fetal membranes than in control cows. This was demonstrated by the accumulation of conjugated dienes, hydroperoxides, and MDA. Formylokinurenine and bityrosine levels, two indicators of the intensity of protein oxidation processes, were higher in cows with placental retention than in those that had the placenta eliminated. The parameter used to determine the extent of DNA oxidation, hydroxyguanine (8OH-dG), was shown to be higher in cows with retained placenta. (Kankofer et al., 1996; Kankofer, 2001a; Kankofer, 2001b; Kankofer, 2001c; Kankofer, 2002).

Data from the literature indicated that there was a distinct pattern during time for cows with and without placental retention when it came to total antioxidant capacity and vitamin A. In general, only cows without placental retention exhibited the prepartum increase in total antioxidant capacity, and those animals' values were slightly greater after parturition and one week after delivery than those from cows with placental retention. The placental tissue's total antioxidant capacity (TAC) was determined right after delivery. Compared to healthy cows, the tissues of cows with placental retention exhibited higher levels of TAC. Compared to cows without placental retention, cows with placental retention showed lower concentrations of vitamin C and

SOD, but higher levels of GPx and CAT activities. The decreased values for TAC in the blood of placental retention-affected cows may point to a redistribution of the total antioxidant capacity in the placental tissue of these cows (Kankofer et. al, 2010).

Vitamin A levels have been demonstrated to increase antepartum and then decrease after one week in cows without placental retention. The vitamin A content in cows with placental retention remained unchanged. Retinol concentrations have been shown to be reduced in postpartum non-retentive cows than in placental retained cows. The different time variations in TAC and Vitamin A in cows with and without retained fetal membranes may indicate that the latter require more antioxidants in order to deal with specific oxidative stress in the placenta, which may have an impact on the placental membranes' proper release (Kankofer et. al, 2010).

CONCLUSION

The scientific literature regarding oxidative stress and reproductive diseases in dairy cows has been highlighted by our review. We believe this information is significant because it is applicable to the areas of animal welfare and reproduction, and it will serve as a basis for future studies that investigate the relationship between oxidative stress, reproduction diseases, and nutrition in the same group of cows.

REFERENCES

1. Albani, K. D., Da Silva, A. S., Machado, G., Bottari, N. B., Alves, M. S., Campigotto, G., Fritzen A., Schetinger M. R. C., Morsch V. M., Zaboot R., Lopes, L. S. (2017). Acta Scientiae Veterinariae, 45(1517), 1-10.
2. Andrei, S., Bunea, A., & Pintea, A. (2014). 3. In Stresul oxidativ şi antioxidanţi naturali (pp. 73-75). Cluj-Napoca: AcademicPres.
3. Baithalu, R., Singh, S., Kumaresan, A., Mohanty, A., Mohanty, T., Kumar, S., . . . Agarwal, S. (2016). Transcriptional abundance of antioxidant enzymes in endometrium and their circulating levels in Zebu cows with and without uterine infection. Animal Reproduction Science, 177, 79-87.
4. Brodzki, P., Brodzki, A., Krakowski, L., Dąbrowski, R., Szczubiał, M., & Bochniarz, M. (2019). Levels of selected cytokines and acute–phase proteins in the serum of dairy cows with cystic ovarian disease and those in follicular and luteal phases of normal ovarian cycle. Research in Veterinary Science, 123, 20-25.
5. Calder, P. C., Dimitriadis, G., & Newsholme, P. (2007). Glucose metabolism in lymphoid and inflammatory cells and tissues. Current Opinion in Clinical Nutrition and Metabolic Care, 10(4), 531-540.
6. Cargile, B., & Tracy, D. (2015). Interaction of Nutrition and Reproduction in the Dairy Cow. In 911038752 716987881 R. M. Hopper (Author), Bovine reproduction (pp. 283-289). Ames, IA: John Wiley & Sons.
7. Contreras, G., O'Boyle, N., Herdt, T., & Sordillo, L. (2010). Lipomobilization in periparturient dairy COWS influences the composition of plasma NONESTERIFIED fatty acids and leukocyte phospholipid fatty acids. *Journal of Dairy Science, 93*(6), 2508-2516.
8. Douglas, G., Rehage, J., Beaulieu, A., Bahaa, A., & Drackley, J. (2007). Prepartum nutrition alters fatty acid composition in plasma, adipose tissue, and liver lipids of periparturient dairy cows. Journal of Dairy Science, 90(6), 2941-2959.
9. Douthwaite, R., & Dobson, H. (2000). Comparison of different methods of diagnosis of cystic ovarian disease in cattle and an assessment of its treatment with a progesterone-releasing intravaginaI device. Veterinary Record, 147(13), 355-359.
10. Elsayed, D. H., Abdelrazek, H. M., El- Azzazi, F. E., Ismail, S. A., & Mahmoud, Y. K. (2020). Hormonal and metabolic profiles related to placental retention with emphasis on oxidative stress and serotonin receptors in pluriparous buffaloes. Reproduction in Domestic Animals, 55(4), 469-478.
11. Herdt, T. H. (2000). Ruminant Adaptation to Negative Energy Balance. Veterinary Clinics of North America: Food Animal Practice, 16(2), 215-230.
12. Kankofer, M. (2001a). The levels of lipid peroxidation products in bovine retained and not retained placenta. Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA), 64(1), 33-36.
13. Kankofer, M. (2001b). Protein Peroxidation Processes in Bovine Retained and Not-retained Placenta. Journal of Veterinary Medicine Series A, 48(4), 207-212.

14. Kankofer, M. (2001c). Antioxidative Defence Mechanisms Against Reactive Oxygen Species in Bovine Retained and Not-Retained Placenta: Activity of Glutathione Peroxidase, Glutathione Transferase, Catalase and Superoxide Dismutase. Placenta, 22(5), 466-472.
15. Kankofer, M. (2002). Placental Release/Retention in Cows and its Relation to Peroxidative Damage of Macromolecules. Reproduction in Domestic Animals, 37(1), 27-30.
16. Kankofer, M., Albera, E., Feldman, M., Gundling, N., & Hoedemaker, M. (2010). Comparison of antioxidative/oxidative profiles in blood plasma of cows with and without retained fetal placental membranes. Theriogenology, 74(8), 1385-1395.
17. Kankofer, M., Lipko, J., & Zdunczyk, S. (2005). Total antioxidant capacity of bovine spontaneously released and retained placenta. Pathophysiology, 11(4), 215-219.
18. Kankofer, M., Podolak, M., Fidecki, M., & Gondek, T. (1996). Activity of placental glutathione-peroxidase and superoxide-dismutase in cows with and without retained fetal membranes. Placenta, 17(8), 591-594.
19. Kimura, K., Goff, J. P., & Kehrli, M. E. (1999). Effects of the Presence of the Mammary Gland on Expression of Neutrophil Adhesion Molecules and Myeloperoxidase Activity in Periparturient Dairy Cows. Journal of Dairy Science, 82(11), 2385-2392.
20. Kimura, K., Goff, J. P., Kehrli, M. E., Harp, J. A., & Nonnecke, B. J. (2002). Effects of MASTECTOMY on composition of peripheral BLOOD MONONUCLEAR cell populations In periparturient dairy cows. Journal of Dairy Science, 85(6), 1437-1444.
21. Kizil, O., Akar, Y., Yuksel, M., & Saat, N. (2010). Oxidative stress in cows with acute puerperal metritis. Revue De Medecine Veterinaire, 161(7), 353-357.
22. Meyer, D. J., & Harvey, J. W. (2004). Veterinary laboratory medicine: Interpretation and diagnosis. St. Louis, MO: Saunders.
23. Nonnecke, B., Kimura, K., Goff, J., & Kehrli, M. (2003). Effects of the mammary gland on functional capacities of blood mononuclear leukocyte populations from periparturient cows. Journal of Dairy Science, 86(7), 2359-2368.
24. O'Boyle, N., Contreras, G., Mattmiller, S., & Sordillo, L. (2012). Changes in glucose transporter expression in monocytes of periparturient dairy cows. Journal of Dairy Science, 95(10), 5709-5719.
25. Ohtsuka, H., Koiwa, M., Hatsugaya, A., Kudo, K., Hoshi, F., Itoh, N., Yokota H., Okada H., Kawamura, S. (2001). Relationship between Serum TNF activity and insulin resistance in dairy cows affected with naturally Occurring fatty liver. Journal of Veterinary Medical Science, 63(9), 1021-1025.
26. Peter, A. T. (2015). Retained Fetal Membranes. In 911062589 717002254 R. M. Hopper (Author), Bovine reproduction (p. 431). Ames, IA: John Wiley & Sons.
27. Plank, L. D., & Hill, G. L. (2000). Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma. World Journal of Surgery, 24(6), 630-638.
28. Raphael, W., & Sordillo, L. (2013). Dietary polyunsaturated fatty acids and inflammation: The role of phospholipid biosynthesis. International Journal of Molecular Sciences, 14(10), 21167-21188.
29. Serhan, C. N. (2009). Systems approach to inflammation resolution: Identification of novel anti-inflammatory and pro-resolving mediators. Journal of Thrombosis and Haemostasis, 7, 44-48.
30. Sharma, N., Singh, N. K., Singh, O. P., Pandey, V., & Verma, P. K. (2011). Oxidative Stress and Antioxidant Status during Transition Period in Dairy Cows. Asian-Australasian Journal of Animal Sciences, 24(4), 479-484.
31. Sordillo, L. M., & Raphael, W. (2013). Significance of Metabolic Stress, Lipid Mobilization, and Inflammation on Transition Cow Disorders. Veterinary Clinics of North America: Food Animal Practice, 29(2), 267-278.
32. Sordillo, L. M., Contreras, G. A., & Aitken, S. L. (2009). Metabolic factors affecting the inflammatory response of periparturient dairy cows. Animal Health Research Reviews, 10(1), 53-63.
33. Sordillo, L., & Mavangira, V. (2014). The nexus between nutrient metabolism, oxidative stress and inflammation in transition cows. Animal Production Science, 54(9), 1204.

34. Suriyasathaporn, W., Heuer, C., Noordhuizen-Stassen, E. N., & Schukken, Y. H. (2000). Hyperketonemia and the impairment of udder defense: A review. Veterinary Research, 31(4), 397-412.
35. Talukder, S., Ingenhoff, L., Kerrisk, K., & Celi, P. (2014). Plasma oxidative stress biomarkers and progesterone profiles in a dairy cow diagnosed with an ovarian follicular cyst. Veterinary Quarterly, 34(2), 113-117.
36. Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal *physiological functions and human disease. The International Journal of Biochemistry & Cell Biology*, *39*(1), 44-84.
37. Vanholder, T., Opsomer, G., & Kruif, A. D. (2006). Aetiology and pathogenesis of cystic ovarian follicles in dairy cattle: A review. Reproduction Nutrition Development, 46(2), 105-119.
38. Yuan, K., Farney, J. K., Mamedova, L. K., Sordillo, L. M., & Bradford, B. J. (2013). Tnfα altered inflammatory responses, impaired health and productivity, but did not affect glucose or lipid metabolism in early-lactation dairy cows. PLoS ONE, 8(11).