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Does Oxidative Stress Impact Bovine Reproductive Disorders?

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ABSTRACT

Oxidative stress indicates an imbalance between pro-oxidants and antioxidants mechanisms of the body. The elevated production of stress level affects physiological functions of female reproduction. Literatures pertaining to oxidative stress have become an active area of research investigation now a day in livestock species particularly in veterinary medicine in general and reproduction in particular. This is because of the increased incidence of infertility problems in livestock and perhaps will remain as emerging area of research in the coming decades. The oxidative stress is surmised to have role in pathophysiology of female infertility. From a clinical perspective, it is of utmost importance to have knowledge in respect to impact of oxidative stress in bovine infertility. This review focuses on the pathogenesis of various bovine reproductive disorders such as cystic condition, endometritis, retained fetal membrane, embryonic mortality and repeat breeding with respect to oxidative stress.

Key words: Oxidative stress, Bovine, Infertility, Pathogenesis, Reactive oxygen species.

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INTRODUCTION

Infertility in female animals is the major hurdle to achieve the optimum reproductive efficiency and productivity of dairy animals. Infertility increases rearing cost and culling rate (Plaizier *et al*., 1998). The culling rate of cattle due to infertility has been reported to be 32.6% (Ansari-Lari *et al*., 2012). In India, the annual culling rate ranges from 18 to 40% cattle due to infertility problems (Maji and Samanta, 2013). Factors such as nutrition, infection, hormone and management have been studied in detail to understand mechanism behind occurrence of infertility (De Rensis and Scaramuzzi, 2003; Veerkamp *et al*., 2003; Givens, 2006; Walsh *et al*., 2011).

Recently, oxidative stress (OS) has become an active area of research investigation in human and livestock reproduction. The oxidative stress (OS) has anticipated role in reproductive abnormalities in animals. Earlier, authors have highlighted possible role of OS in occurrence of summer acyclicity (Jan et al., 2011), follicular cysts (Khan et al., 2011), ovarian acyclicity (Khan and Das, 2011), delayed puberty (Kumawat, 2014), uterine infection (Pande *et al*., 2013) and repeat breeding

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syndrome (Prabaharan *et al*., 2014).The available literature impels to understand the patho-physiology of OS in female infertility so that specific antioxidant therapies could be designed to control reproductive disorders. In the present paper, an overview of oxidative stress in relation to female infertility in dairy animals has been discussed.

The reactive oxygen species (ROS) are the metabolic end products of cellular process. The ROS are highly reactive and result in cellular damage and disease (Agarwal *et al*., 2005). ROS can be categorized into two groups: free oxygen radicals and non-radical ROS. Free oxygen radicals include superoxide ($O_2\bullet^-$), hydroxyl radical ($\bullet OH^-$), nitric oxide (NO•). While, non-radical ROS include hydrogen peroxide (H_2O_2), singlet oxygen (^1O), ozone/trioxygen (O_3) compounds (Liou and Peter Storz, 2010).

The body is persistently attacked by the ROS which is generally controlled by antioxidant system. There are two types of antioxidants: enzymatic and non-enzymatic. Enzymatic antioxidants possess a metallic center, and they transfer electrons to balance molecules for the detoxification process. Endogenous antioxidant enzymes include superoxide dismutase (SOD), catalase, glutathione peroxidase (GPX), and glutathione oxidase. The non-enzymatic antioxidants consist of dietary supplements and synthetic antioxidants such as vitamin C, taurine, hypotaurine, vitamin E, zinc (Zn), selenium (Se), betacarotene, and carotene (Sharma and Agarwal, 2004). The state of stress occurs either when level of oxidation exceeds antioxidants or when subpar level of antioxidants is unable to scavenge normal level of ROS produced.

The ROS are considered as double-edged swords. At low concentration, the ROS have role in functioning of various physiological processes but have deleterious effect on cellular components at high concentration (Birben *et al*., 2012).

MECHANISM OF ROS INDUCED INJURY

Reactive oxygen species target the cellular macromolecules such as lipids, proteins and nucleic acids and ultimately resulting in cellular death.

***Per-oxidative damage to lipids*:** Lipids containing polyunsaturated fatty acids (PUFA) are target sites for ROS. The lipid peroxidation (LPO) damage cell membrane, inactivate cellular proteins and generate lipid-derived radicals which further damage cellular component. Therefore, LPO is a self-propagating reaction unless it is counteracted by antioxidants.

***Protein modification*:** Amino acids are the target for oxidative damage (Agarwal *et al*., 2012). The oxidation of side chains leads to the generation of carbonyl groups. The oxidation results in abnormal folding, protein aggregation, loss of function and cellular death (Burton and Jauniaux, 2011). The oxidative changes in enzymes inhibit their physiological activities (Fucci *et al*., 1983).

***Mitochondrial alteration*:** Mitochondria are one of the main sites for production of ROS (Lenaz, 2001) due to presence of O_2^- in electron transport chain. These cell organelles are prone to get attacked by ROS due to lack of histone protection and absence of repair mechanism.

***Per-oxidative DNA (Deoxy-ribonucleic acid) damage*:** The reaction between ROS and nitrogenous bases or deoxy-ribose sugars of DNA usually results in oxidatively modified products in DNA. The oxidative impact on sugar moieties could cause breakage in strand while effect on histone protein may interfere with chromatin folding and DNA repair (Burton and Jauniaux, 2011). The presence of these altered nitrogenous bases affects replication and transcription processes and results in mutations and altered gene expressions (Cooke *et al*., 2003).

PATHO-PHYSIOLOGY IN FEMALE REPRODUCTION

The oxidative stress certainly has role in the etiology of bovine diseases including reproductive disorders. Although pathogenesis is not clear; the role is evident by supplementation with certain antioxidants resulting in amelioration of diseases (Hajhashemi *et al*., 2010).

Cystic ovarian disease/degeneration (COD)

Cystic ovarian disease/degeneration (COD) is one of the most common reproductive disorders chiefly found in high milk yielder cows. The role of oxidative stress in the pathogenesis of COD has been documented in earlier literature (Rizzo *et al*., 2009). The reactive oxygen species serve as key factor during ovulatory process. A strict interplay exists between ROS, apoptosis, and ovulation. During ovulation, ovarian epithelium undergoes apoptosis with subsequent weakening of the follicular wall leading to ovulatory rupture (Murdoch and Gottsch, 2003). However, the pathological increase in concentration could hinder the ovulation. Jan *et al*. (2015) reported an altered serum concentration of antioxidants/oxidant in buffalo with COD. The similar inclination was observed in follicular fluid of affected as compared to healthy buffaloes. This indicates

inefficient antioxidant mechanism in follicular micro-environment in cystic animals. Further, it might be possible that oxidative disturbance in follicular environment damages granulosa cells and thereby rendering them unresponsive to gonadotropin surge.

On contrary, lower ROS level in the follicular fluid of cystic cows has been reported than the healthy cows by Rizzo *et al*. (2009). The author concluded that the low concentration may be insufficient to induce apoptosis of the follicular cells, thus inhibiting ovulation. The alteration in remodeling of extracellular matrix was observed in cystic follicles. The remodeling involves matrixmetalloproteinases (MMPs) expression mediated by ROS and is necessary for ovulation (Imai *et al*., 2003). This stipulate that poor ROS level might also be responsible for anovulation. The pathogenesis involving ROS in COD is two-sided. The information is yet to be perceived however, it can be said that disruption between oxidant and antioxidant balance prevents the necessary physiological responses involving the follicle rupture and hence ovulation.

Postpartum anestrus

During transition period cows experience oxidative stress, this may contribute to peri-parturient disorders including postpartum anestrus. Besides negative energy balance the increased level of stress is found to be associated with postpartum anestrus (Pedernera *et al*., 2010).

The ovarian function is regulated by the balance between oxidant and antioxidant (Khan and Das, 2012). However, aberration in the balance can result into the functionally inactive ovaries. The follicular development is a continuous process and number of follicles is observed even during acyclicity (Baruselli *et al*., 2004). However, final growth is impeded due to oxidative stress resulting into anestrus. The ROS are involved in initiation of apoptosis in antral follicles by influencing the folliculogenesis and the steroidogenesis (Ciani *et al*., 2015). When the follicle grows oxidative stress may hamper the synthesis of proteins and RNA required for its development (Derar *et al*., 2011). The low level of ascorbate and high level of nitric oxide (NO) in follicular fluid of atretic follicles were observed by Khan and Das (2012). Hence, evident damaging effect of ROS on oocyte growth and maturation, follicular steroidogenesis resulting into acyclicity.

The oxidants hamper ovarian steroidogenesis as manifested by decrease serum concentration (Elsayed *et al*., 2019). The ROS induces apoptotic protein expression resulting in DNA fragmentation and granulosa cell apoptosis (Tripathi *et al*., 2013). The granulosa cell apoptosis reduces estradiol level by inhibiting aromatase activity (Dunnam *et al*., 1999). The low level of estrogen affects follicular development and hinders estrogen-regulated selection process (Beg and Ginther, 2006). The apoptosis further results in the disruption of gap junctions between granulosa cells and oocyte. The poor cell to cell communication deprives oocyte from nutrients and therefore undergoes atresia.

Summer anestrus

The effect of high environment temperature on bovine fertility is well established. The exposure further predisposes bovine population to oxidative stress. Higher level of oxidative stress has been reported in summer anestrus buffalo (Kumar *et al*., 2015). The generated oxidants modulate gonadotropic and steroidiogenic properties, poor estrus expression or cessation of estrous cycle. The imbalance between oxidant and antioxidant in follicular microenvironment due to heat stress possibly impairs follicular growth and development results in acyclicity. High concentration of NO (467 vs 265 μM/ml) and low concentration of ascorbic acid (9 vs 13 μg/ml) has been reported in acyclic as compared to cyclic buffalo during summer season (Jan *et al*., 2011). Higher NO level presumably affects aromatase activity leading to lower estradiol concentration. The resultant low estrogen level leads to lack of estrus expression in such animal. Further, the estrogenically inactive morphologically dominant follicles fail to stimulate the much needed luteinizing hormone (LH) surge, thus resulting in anovulatory anestrus or acyclicity (Das and Khan, 2010). The treatment with antioxidant such as melatonin has been found to resume cyclicity in buffalo with summer anestrus (Kumar *et al*., 2015). This additionally indicates the relation between summer anestrus and oxidative stress.

Repeat breeding

Repeat breeding is a multifactorial condition; therefore, multifarious role of oxidative stress could be anticipated. Oocyte metabolism and steroid production causes an increase in ROS generation (Ciani *et al*., 2015). The resultant oxygen deprivation is necessary for stimulation of angiogenesis and follicular growth and development. The equilibrium is maintained by antioxidant system however, uncontrolled release of ROS results into stress. The resultant oxidative stress damages nucleic acid, protein and lipids (Forman and Torres, 2002) and thus impairing

oocyte quality. Oxidative damage to the oocyte has been implicated as a cause of persistently poor oocyte quality. Stress may determine an overproduction of free radicals, which attack polyunsaturated fatty acids, thus causing an alteration of lipoproteins, resulting in alterations in progesterone production.

The abnormal concentration of oxidants such as NO may lead to retention of the ovum and delayed sperm transport due to its relaxing effect on smooth muscles. This is evident by increased MDA and NO in buffalo with repeat breeding syndrome by Ahmed *et al*. (2010). The ROS impair luteinizing hormone receptors (Vega et al., 1995) or inhibit the translocation of cholesterol to the mitochondria (Behrman and Aten, 1991) or cytochrome $P450_{scc}$ enzyme activity (Carlson et al., 1995). Further, free radicals activate phospholipase A2; hence are involved in corpus luteum lysis (Ciani *et al*., 2015). The ROS restrict the progesterone production by corpus luteum (Carlson *et al*., 1995). The oxidants uncouple LH receptor from adenylate cyclase and inhibit steroidogenesis by interrupting trans-mitochondrial cholesterol transport (Behrman and Aten, 1991). The reduction in progesterone secretion leads to the embryonic or fetal death. The decrease in embryonic mortality following antioxidant therapy was perceived by Prabhaharan *et al*. (2015). The study found positive correlation between decreased LPO and increased serum antioxidants level with conception rate. Therefore, it is imperative that oxidative stress results into fertilization failure or early embryonic death.

Endometritis

The endometritis is the inflammation of endometrium affecting about 7.5 to 40% bovine population (Gilbert *et al*., 2005). The susceptibility of uterine infection is interrelated with oxidative stress level was reported by Heidarpour *et al*. (2012).The high ROS level in nutrient deficient animal makes them susceptible due to poor immunity.Under the state of negative energy balance (NEB); non-esterified fatty acids (NEFA) are released. The subsequent oxidation of NEFA increases ROS generation (Li *et al*., 2016). The free radicals damage epithelial cells barrier resulting in tissue injury permitting pathogen invasion. Higher blood levels of NEFA suppress immune function which further increases susceptibility of uterine infection (Ster *et al*., 2012).

Additionally, inflammatory diseases enhance oxidative reaction and reduce antioxidant defense capabilities. The uterine infection and inflammation lead to increased oxidants level. The higher ROS is released from stimulated neutrophils or pro-inflammatory cytokines in response to bacterial invasion (Krishnan *et al*., 2014). Further, decreased blood concentration of antioxidants has been observed by Rautela *et al*. (2018) in cows affected with endometritis. This indicates exhaustion of endogenous antioxidant while counteracting the oxidants. An imbalance between antioxidant and oxidant in nutrient deficient animal makes it susceptible for infection. The resultant infection and inflammation further aggravate the condition bringing out the infertility.

Retained fetal membrane (RFM)

The retained fetal membrane (RFM) is postpartum disorder that has negative impact on reproductive efficiency of an animal. The relation between antioxidants, oxidants and RFM has been reported in various studies (Kankofer *et al*., 2010).The high level of LPO has been perceived in cows with RFM as compared to normal cows (Gupta *et al*., 2005). Similarly, high level of malondialdhyde (MDA) and low level of total antioxidant capacity (TAC) has been observed in RFM affected buffalo. Further, the study reported that the changes in glutathione peroxidase level negatively affect the PMN function leading to increase incidence of RFM (Aziz *et al*., 1984).

Although, the pathogenesis due to oxidative stress is not clearly understood, the involvement of oxidative stress in the etiology of RFM is suggested by the reduced incidence when the antioxidants were supplemented. An association between poor antioxidant status, compromised function of leukocyte and increased risk of RFM has been documented in earlier literatures (Kimura *et al*., 2002). The lack of leukocyte activity between feto-maternal placental junction leads to 100% incidence of RFM as the leukocytes release proteolytic enzymes that play a role in detachment of placenta. In accordance, Allison and Laven (2000) reported the alterations in leukocyte activity following supplementation of antioxidant (vitamin E) with reduced prevalence of RFM. Therefore, it is not incorrect to state that poor immune function and reduced lymphocyte chemotaxis in cows undergoing oxidative stress predispose to RFM.

CONCLUSIONS

Reactive oxygen species have a dual role in the female reproductive tract. They serve as key signal molecules in physiological processes such as follicular development, ovulation, luteolysis and initiation of parturition but also can be considered cofactor in pathological process. Oxidative stress result from over production of ROS in relation to antioxidant defense level. The effects of free radical on gamete

production, steroidogenesis and embryonic development have been implicated in poor reproductive performance of an animal. The knowledge of the physiological and pathological ROS concentrations could be very useful in the suggestions about dietary integrations, employment of antioxidants, to improve health and fertility of animal.

CONFLICT OF INTEREST

None of the authors has conflict of interest to declare.

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