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Antioxidant supplementation in female ruminants during the periconceptional period: A review¤

Suplementación con antioxidantes en hembras rumiantes durante el periodo periconcepcional: Revisión de literatura

Suplementação de antioxidantes em fêmeas de ruminantes durante o período periconcepcional: Revisão de literatura

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Abstract

Oxidative stress is the result of an imbalance between free radicals and antioxidants. Under normal physiological conditions, free radicals are involved in reproductive events such as cell cycle activation, ovulation and luteolysis. However, when an overproduction of free radicals surpasses antioxidant capacity, oxidative damage, reproductive anomalies and diminished fertility occur. Supplementation with antioxidants prevents oxidative damage and can be incorporated into reproductive management to improve fertility in females. Selection of the preovulatory follicle, ovulation, fertilization, embryo development and formation of the corpus luteum occur during the periconceptional period. This is a dynamic period and the events are susceptible to oxidative stress damage. Therefore, the objective of this review is to discuss the effect of oxidative stress on reproductive events during the periconceptional period, as well as to address antioxidant supplementation during this period.

Key words: *embryo, fertility, free radicals, oocytes, ovulation, oxidative stress.*

Resumen

El estrés oxidativo es generado por un desbalance entre radicales libres y antioxidantes. Bajo condiciones fisiológicas normales, los radicales libres participan en eventos reproductivos tales como activación del ciclo

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celular, ovulación y luteólisis. Sin embargo, cuando estos son producidos en cantidades que sobrepasan la capacidad antioxidante del organismo producen daño oxidativo y trastornos reproductivos que disminuyen la fertilidad de la hembra. La suplementación con antioxidantes previene el daño oxidativo y su incorporación a programas de manejo reproductivo puede ser una opción para mejorar la fertilidad de la hembra. La selección del folículo preovulatorio, ovulación, fecundación, desarrollo embrionario y formación del cuerpo lúteo ocurren durante el periodo periconcepcional. Este es un periodo dinámico y los eventos que ocurren en él son susceptibles a daño por estrés oxidativo. Por tanto, el objetivo de esta revisión es discutir el efecto del estrés oxidativo en los eventos reproductivos durante el periodo periconcepcional, así como la suplementación de antioxidantes en rumiantes durante este periodo.

Palabras clave: *embrión, estrés oxidativo, fertilidad, ovocito, ovulación, radicales libres.*

Resumo

O stress oxidativo é gerado por um desequilíbrio entre radicais livres e antioxidantes. Sob condições fisiológicas normais, os radicais livres participam de eventos reprodutivos, como ativação do ciclo estral, ovulação e luteólise. No entanto, quando é produzido em quantidades que excedem a capacidade antioxidante do organismo, produzem danos oxidativos e distúrbios reprodutivos que diminuem a fertilidade da fêmea. A suplementação com antioxidantes previne o dano oxidativo e sua incorporação em programas de gerenciamento reprodutivo pode ser uma opção para melhorar a fertilidade da fêmea. A seleção do folículo pré-ovulatório, ovulação, fecundação, desenvolvimento embrionário e formação do corpo lúteo ocorrem durante o período periconcepcional. Este é um período dinâmico e os eventos que ocorrem são suscetíveis ao dano por estresse oxidativo. Portanto, o objetivo dessa revisão é fornecer ao leitor conhecimento sobre o efeito do estresse oxidativo em eventos reprodutivos durante o período periconcepcional, e também discutir a suplementação com antioxidantes em ruminantes durante este período.

Palavras-chave: *embrião, estresse oxidativo, fertilidade, ovócito, ovulação, radicais livres.*

Introduction

Oxidative stress is defined as an imbalance between free radicals and antioxidants, caused by an increased production of the former or decreased concentrations of the latter (Halliwell and Whiteman, 2004). A free radical is a highly reactive atom or molecule that contains one or more unpaired electrons in its outer orbit, and extracts an electron from other compound to gain stability (Phaniendra *et al.,* 2015). Reactive oxygen species (ROS), and reactive nitrogen species are the main types of free radicals (Agarwal *et al.,* 2005). They are normally produced in the mitochondria, peroxisomes, during inflammation and phagocytosis (Lobo *et al.,* 2010). Free radicals participate in diverse physiological processes without causing harm, but high concentrations can cause oxidative stress and damage to lipids, proteins and DNA (Silva and Coutinho, 2010). In farm animals, heat stress, dietary imbalances and bacterial infections can increase free radical production and oxidative stress (Celi and Gabai, 2015).

Antioxidants prevent or inhibit oxidation of the substrate (lipids, protein or DNA) by donating electrons (Halliwell and Gutteridge, 1995). Antioxidants can be classified as enzymatic and non-enzymatic. Enzymatic antioxidants include superoxide dismutase, catalase, glutathione peroxidase and glutathione oxidase, while the non-enzymatic group includes vitamins A, C and E, beta-carotene, and trace elements such as copper, manganese, selenium and zinc, which are cofactors of antioxidant enzymes (Leung, 1998; Agarwal *et al.*, 2012; Pisoschi and Pop, 2015).

Free radicals are normally involved in reproductive events such as follicular development, ovulation, corpus luteum development, luteolysis and early embryo development (Rizzo *et al.,* 2012). However, an imbalance between free radicals and antioxidants can cause failure to conceive. Reactive oxygen species are part of the mechanism controlling ovulation; failure to achieve enough intra-follicular concentrations to produce preovulatory follicle rupture causes follicular cyst in cattle (Rizzo *et al.,* 2009; Talukder *et al.,* 2014a). Talukder *et al.* (2015) reported that cows with ovulatory oestrous cycles have greater concentrations of superoxide dismutase and lower oxidative damage to lipid products than cows that did not ovulate. In addition, repeat breeder cows that fail to conceive after artificial insemination have higher serum concentrations of oxidative stress markers than pregnant cows (Rizzo *et al.,* 2007). In this regard, Celi (2011) mentions that oxidative stress indicators are higher in cows experiencing late embryo mortality. In buffalos, blood concentrations of antioxidants vitamin E and β-carotene were lower and intra-follicular concentrations of ROS were higher in animals in anestrus than those with normal oestrous cycles (Kahlon and Singh, 2004; Jan *et al.,* 2014).

Oxidative stress occurs during different periods in animal systems, and antioxidants can be supplemented to improve reproductive performance (Nayyar and Jindal, 2010). In this review, we are focused on the periconceptional period; which comprises the events preceding, during and immediately occurring after conception (Louis *et al.,* 2008). These events include follicle wave emergence, preovulatory follicle selection, ovulation, fecundation, early embryo development and corpus luteum formation. Restriction to these events is because available hormone treatments allow controlling these events, and the time of occurrence can be predicted (Lucy *et al.,* 2004; Rahman *et al.,* 2008; Menchaca *et al.,* 2017). Therefore, if oxidative stress is suspected during the occurrence of events in this period, antioxidants can be supplemented to specifically protect/improve such events. The objective of this review is to provide evidence of the impacts of oxidative stress during the periconceptional period. In addition, the effect of antioxidant supplementation during hormonal treatments in female ruminants will be addressed.

Effects of oxidative stress on preovulatory follicle development and oocyte competence

Follicles undergo primordial, primary, small preantral, large preantral and small antral stages before reaching the preovulatory stage (Braw-Tal and Yossefi, 1997). Mammalian females are born with a fixed number of primordial follicles from which a preovulatory follicle will be recruited. There are two types of follicular recruitment: initial and cyclic. Initial recruitment is a continuous process in primordial follicles that occurs before puberty, while cyclic recruitment starts after puberty under the control of increased gonadotropin production (McGee and Hsueh, 2000). After puberty, antral follicles are recruited in a predictable wave fashion between estruses (Adams *et al*., 2008). The follicle wave is preceded by a FSH surge, which allows cyclic antral follicle recruitment (Fortune *et al*., 2001). After recruitment takes place, selection and growth of the dominant follicle occurs under the influence of LH until the ovulatory stage occurs (Ginther, 2000). For a follicle to accomplish the dominant status, it must be capable of performing three fundamental tasks: expressing gonadotropin receptors, performing steroidogenesis, and having access to IGF-I (Quirk *et al*., 2004). Under conditions of declining progesterone production, such as luteolysis, the dominant follicle will reach the ovulatory stage. The time required for a primordial follicle to reach the ovulatory stage is at least 80 days (Britt, 2008). During this period, the follicle and its enclosed oocyte are exposed to harmful conditions such as oxidative stress.

The oocyte from the primordial follicle to the preovulatory stage is arrested at the diplotene stage of prophase I. The preovulatory surge of LH breaks diplotene arrest by reducing the intra-oocyte concentration of cyclic 3′,5′-adenosine monophosphate (cAMP) (Tripathy *et al.,* 2010), which is associated with a rise in the intra-oocyte concentration of hydrogen peroxide (H_2O_2) (Pandey and Chaube*,* 2014). The intra-oocyte generation of a tonic level of H_2O_2 is necessary to exit diplotene stage arrest, but high concentrations of H_2O_2 produce oocyte apoptosis (Chaube *et al.,* 2005; Tripathi *et al.,* 2009). The H_2O_2 is part of the ROS family. It is generated after the dismutation of superoxide radical by superoxide dismutase and can then be scavenged by glutathione peroxidase or catalase (Valko *et al.,* 2007). Potential intra-follicular sources of reactive oxygen species include steroidogenesis (Hanukoglu *et al*., 1993), leukocytes (Brännström and Enskog, 2002) and ATP generation by mitochondrial electron transport (Kala *et al.,* 2016). In addition, the preovulatory peak of LH induces an increase in ROS production (Yacobi *et al*., 2007), which is necessary to accomplish ovulation (Shkolnik *et al*., 2011).

Embryo implantation is reduced when the oocyte comes from a follicle with a high percentage of granulosa cells producing ROS (Jancar *et al.,* 2007). Apoptosis, induced by oxidative stress to granulosa cells (Shen *et al.,* 2012), implies a reduction in nutrient supply and signal molecules to the oocyte (Kidder and Vanderhyden, 2010), which can disrupt oocyte meiotic maturation (Ratchford *et al.,* 2008). Additionally, ROS causes DNA fragmentation, cell cycle arrest, and apoptosis (Chaube *et al.,* 2005; Prasad *et al.,* 2016). Thus, on one hand, a moderate increase in ROS production is used as a signal to break cell cycle arrest, but on the other, high concentrations disrupt oocyte quality. It is likely that the required amount of ROS within the follicle and oocyte is regulated, at least in part, by the intra-follicular antioxidant system.

The presence of antioxidants such as catalase, glutation peroxidase, superoxide dismutase, ascorbic acid, vitamin E, and β-carotene has been demonstrated in ruminant follicle compartments (Schweigert and Zucker, 1988; Behl and Pandey, 2002; Combelles *et al.,* 2010; Gupta *et al.,* 2011; Hennet *et al.,* 2013; Hozyen *et al.,* 2014). Antioxidants prevent oxidative damage by preventing ROS concentrations from reaching levels that could harm the follicle and oocyte. However, situations leading to increased ROS production or to a reduction in antioxidant concentrations are likely to affect fertility by causing oxidative damage. Examples of these situations are mastitis, negative energy balance and heat stress.

Mastitis causes a 26 to 28% reduction in conception rates when it occurs within 10 days before or 30 days after artificial insemination (Lavon *et al.,* 2011). The reduced pregnancy rate after mammary gland infection can be explained by alterations in ovarian steroid production and gonadotropin secretion (Wolfenson *et al.,* 2015). In addition, mastitis produces an imbalance between antioxidants and oxidants, leading to oxidative stress (Sharma *et al.,* 2016; Shahid *et al.,* 2017). Recently, it was found that cytoplasmic maturation and embryo viability is compromised when oocytes are cultured with follicular fluid from cows with mastitis (Roth *et al.,* 2015). Mastitis is experimentally induced by injection of gram negative toxins, such as lipopolysaccharides (Asaf *et al.,* 2014). Lipopolysaccharides disrupt follicular steroidogenesis by reducing the expression of gonadotropin receptors and steroidogenic enzymes (Magata *et al.,* 2014), inducing apoptosis and oxidative stress in oocytes (Zhao *et al.* 2017). Moreover, mastitis decreases antioxidant blood concentrations and increases oxidant capacity in milk (Kizil *et al.* 2007; Atakisi *et al.,* 2010). Thus, oxidant/antioxidant balance is compromised during mastitis infection.

The increase in milk production after parturition demands a great amount of nutrients, but the inability to consume the required quantity produces a negative energy balance. Thus, the body removes nutrients from internal reserves to sustain vital functions and milk production. The state of negative energy balance is characterized by weight loss, increase in blood concentrations of non-esterified fatty acids (NEFA) and ketone bodies such as beta-hydroxybutyrate (Adewuyi *et al*., 2005).

Negative energy balance can last for 10-12 weeks after calving, during which fertility is compromised (Butler, 2003). After analyzing the NEFA profile and β-hydroxybutyrate in blood serum and follicular fluid of cows after parturition (Leroy *et al.,* 2004), Leroy *et al.* (2005; 2006) found that administration of these two metabolites to the culture medium reduces oocyte competence. Moreover, Van Hoeck *et al.* (2013) reported that oocyte redox status is affected by NEFA, suggesting that oxidative stress induced by NEFA is responsible for lowering oocyte competence in dairy cattle undergoing negative energy balance. In this regard, Song *et al.* (2014; 2016) reported that NEFA and β-hydroxybutyrate cause hepatocyte apoptosis by means of oxidative stress. In addition, cows showing signs of negative energy balance -such as body weight lost, increased concentrations of NEFA and β-hydroxybutyrate- suffer oxidative stress (Bernabucci *et al.,* 2005; Pedernera *et al.,* 2010), which can be explained by diminished blood and follicular concentrations of antioxidants such as β-carotene, vitamins C and E, superoxide dismutase, and glutathione peroxidase (Cigliano *et al.,* 2014; De Bie *et al.,* 2016).

Oxidative stress induced by heat stress disrupts fertility in dairy cattle (Roth, 2015). Heat stress increases ROS production and reduces the proportion of oocytes that attain nuclear maturation and the blastocyst formation rate (Nabenishi *et al.,* 2012). In addition, Takahashi (2012) suggests that oxidative stress induced by high temperatures creates adverse intraoviductal conditions for oocytes, sperm and embryo. Even though antioxidant supplementation seems to be a feasible way of ameliorating the negative effect of heat stress in fertility (Hansen, 2013), De Rensis *et al.* (2017) concluded that more research is needed to identify an antioxidant regimen that can effectively protect oocytes from heat stress.

Effects of oxidative stress on sperm, corpus luteum development and embryo viability

Fertilization of the ovulated oocyte, formation of the corpus luteum and embryo cleavage occur after ovulation. As with the oocyte, reactive oxygen species are necessary for the sperm to achieve capacitation, but high concentrations are detrimental (Aitken *et al.,* 2012). Sources of ROS in the sperm include mitochondria, cytosolic L-amino acid oxidases, and plasma membrane nicotinamide adenine dinucleotide phosphate oxidases (Aitken, 2017). Infertile men have been found to have higher concentrations of reactive oxygen species, lower concentrations of vitamin E, and lower total antioxidant capacity than fertile men (Benedetti *et al.,* 2012). In cattle, oxidative stress induced by heat stress reduces the fertilization rate in dairy cattle during summer season relative to winter (Sartori *et al.* 2002).

An antioxidant system supports corpus luteum functionality. Luteal superoxide dismutase and vitamin C concentrations increase as the corpus luteum develops (Luck and Zhao, 1993; Vu *et al*., 2013), and an increase in luteal antioxidant activity has been reported during pregnancy (Al-Gubory *et al*., 2004). An antioxidant system is necessary to counteract the ROS generated by steroidogenic cells and mononuclear phagocytes (Kato *et al*., 1997), or by the inner environment of the corpus luteum. This is relevant since the mechanism used by $PGF_{2\alpha}$ during luteolytic events implies the production of ROS and a decrease in antioxidant activity (Hayashi *et al*., 2003; Vu *et al*., 2012; Vu *et al*., 2013), resulting in low progesterone production.

A changing antioxidant status is detectable throughout the estrous cycle. According to Aydilek *et al*. (2014), total antioxidant activity is lower in the luteal than in the follicular phase of the estrus cycle in cows. Repeat breeder cows have higher concentrations of ROS during the crucial period of corpus luteum survival (days 12 and 16 of the estrous cycle), causing failure to conceive (Rizzo *et al*., 2007). However, a failure to generate enough ROS after induced luteolysis by PGF2α results in anovulation (Talukder *et al*., 2014b). This suggests that increased antioxidant activity during the luteal phase may be detrimental to reproductive performance in empty cows, but not for pregnant cows.

Oxidative stress is detrimental to embryo survival either by blocking progesterone supply or by a direct effect on embryo cells. The source of reactive oxygen species may come from metabolic activity of the embryo itself (Gupta *et al*., 2006) or from the maternal environment (Poston *et al*., 2011). Regarding the latter, it is known that maternal heat stress is responsible for induced embryonic death by increasing ROS production and antioxidant depletion, but not by heat stress itself (Ozawa *et al*., 2002). When ROS become uncontrolled, they cause morphological and functional alterations, which may block embryo development or apoptosis (Guérin *et al*., 2001), supporting the suggested implication of ROS in bovine embryo mortality (Celi *et al*., 2011).

The early embryo may be capable of developing some degree of resistance to the adverse effects of ROS as it grows. Ealy *et al*. (1993) reported that Holstein cow embryos become less susceptible to maternal heat stress after one day of pregnancy. Similarly, Morales *et al*. (1999) reported that nine- to 16 cell- embryos are more resistant to ROS insults than zygotes and blastocysts. Bain *et al*. (2011) suggested that susceptibility of the bovine embryo to ROS increases during the first 72 hours of embryonic life. In addition, differences in ROS resistance related to embryo sex have been reported (Pérez-Crespo *et al*., 2005); female embryos are more resistant than male embryos. These findings suggest that severity of ROS-induced embryo damage is developmental and sex dependent.

Antioxidant supplementation during the periconceptional period in female ruminants

Oocyte and embryo well-being can be compromised by oxidative damage generated as the result of common reproductive practices around the periconceptional period. Rectal palpation and artificial insemination are stressful to dairy cattle (Nakao *et al*., 1994) and cause oxidative stress (Cingi *et al*., 2012). These practices are commonly and repeatedly performed during estrus synchronization. A common practice among reproductive technicians, before artificial insemination, is to stimulate the reproductive tract via rectal massage for visualization of cervical mucus in order to reveal any infection. However, unexperienced technicians may cause rectal irritation, evidenced by the presence of blood on the palpating hand. This situation is also observed after multiple, prolonged or rough palpations, but it is unknown how much this can affect fertility.

Estrus synchronizations using progesterone-releasing devices is common in small ruminants and cattle. Several studies have reported inflammatory responses and changes in normal flora and vaginal histology of ewes and cattle after using estrus synchronization devices (Manes *et al*., 2010; Suárez *et al*., 2006; Walsh *et al*., 2007; Manes *et al*., 2015). In addition, Sönmez *et al*. (2009) reported a steady increase in ROS after intravaginal sponge insertion in goats, suggesting that sponge insertion can cause oxidative stress. The inflammatory response and oxidative stress induced by insertion of progesterone release devices may be responsible for the reduced fertility in ewes carrying intravaginal sponges (Manes *et al*., 2014).

Ovarian superstimulation of small and large ruminants is used to increase the number of oocytes and embryos that a female would normally produce during a normal estrous cycle. However, superstimulation is known to upregulate genes related to oxidative stress in cattle (Dias *et al*., 2013). In mice, an increase in oxidative damage in the uterus and oviduct (Park *et al*., 2015), as well as a reduction in oocyte mitochondria number and function, have been reported after single and repeated superstimulation. In addition, low quality oocytes -resulting in embryos with mitochondrial functional defects, which are more susceptible to oxidative damage- have been found during superstimulation (Komatsu *et al*., 2014). Since an oxidative insult is present during superstimulation, antioxidant supplementation may help to overcome some of the detrimental effects on oocyte and embryo quality. According to Liu *et al*. (2013) and Ben-Meir *et al*. (2015), antioxidant supplementation not only counteracts oxidative damage in the oocyte but also restores mitochondrial function.

The evidence suggests that antioxidant supplementation may be beneficial, by improving fertility during the periconceptional period. Evidence validating the effectiveness of antioxidant supplementation during hormonal treatment in ruminant females around this period is shown in Table 1. Parenteral antioxidant supplementation is probably the best option during the periconceptional period. As shown in Table 1, antioxidants were given via injection in all cases, probably because high concentrations in blood and other body compartments can be reached faster than through feed supplementation. In the case of vitamin E, for example, parenteral supplementation is a more effective way to improve antioxidant status in the short term compared with in-feed supplementation (Bourne *et al*., 2007; Mokhber-Dezfouli *et al*., 2008). This is relevant because a rapid effect is desired.

Table 1. Effect of antioxidant injection during the periconceptional period on ruminant fertility.

Animal model and antioxidant supplemented	Time of supplementation	Effect	Authors
Dairy cattle injected with 3,000 IU of vitamin E and 3,000 mg of vitamin C	Three days after intravaginal devise insertion, at estrus, and two days after artificial insemination	Increased number of cows pregnant	Gonzalez-Maldonado *et al.,* 2017
Dairy Holstein cows injected with 840 mg of vitamin E and 8 mg of sodium selenite	Just before ovisynch protocol began	Increased antioxidant activity and progesterone production	Yildiz *et al*., 2015
Goats injected with 200 mg of vitamin E	At intravaginal sponge removal and at artificial insemination	Increased multiple births and prolificacy	Sönmez *et al*., 2009
Superovulated Holstein cows injected with 1200 mg of β-carotene and 750 mg of tocopherol	At the time of norgestomet ear implant insertion for estrus synchronization and at first superovulation injection	Increased total viable embryos	Sales *et al*., 2008
Superovulated ewes injected with 500,000 IU of all-trans retinol	On the first and last day of FSH injections	Increased percentage of hatched blastocyst	Eberhardt *et al*., 1999
Ewes injected with 2100 IU of vitamin E	-12, -2, 10, 24 and 48 h with respect to $PGF_{2\alpha}$ injection	Protection of corpus luteum from $PGF_{2\alpha}$ induced luteolysis	Vierk *et al*., 1998

In conclusion, free radicals participate in reproductive events occurring during the periconceptional period. However, situations leading to overproduction that surpasses antioxidant capacity cause oxidative stress and compromise fertility. Antioxidant supplementation during hormonal treatments carried out during this period can improve fertility in female ruminants.

Conflicts of interest

The authors declare they have no conflicts of interest with regard to the work presented in this report.

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