ARTIGO ORIGINAL

Effects of oxidative stress during human and animal reproductions
A review

[1] Carolina B. Berchieri-Ronchi
[1] Paula T. Presti
[1] Ana Lucia A. Ferreira *
[2] Camila R. Correa
[2] Daisy Maria F. Salvadori
[3] Débora C. Damasceno
[3] Kyung-Jin Yeum

[1] Department of Internal Medicine, Botucatu Medical School, Sao Paulo State University (UNESP), Botucatu, SP, Brazil;
[2] Department of Pathology, Botucatu Medical School, Sao Paulo State University (UNESP), Botucatu, SP, Brazil;
[3] Department of Gynecology and Obstetrics, Botucatu Medical School, Sao Paulo State University (UNESP), Botucatu, SP, Brazil;
[4] Division of Food Bioscience, College of Biomedical and Health Sciences, Konkuk University, Chungju-si, South Korea

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ABSTRACT

Given its high ability to damage important cellular components (lipids, proteins and deoxyribonucleic acid), oxidative stress is now recognized as one of the most common mechanisms associated with development of a variety of diseases and natural events such as pregnancy. During reproduction period, there is a change in the pro-oxidant and antioxidant balance due to the body and circulation modifications that are inherent to the pregnancy process. The present paper discusses the role of oxidative stress on the reproduction process. More effective defense strategies are needed to decrease the deleterious effects of oxidative-stress-induced gestation. This approach could be achieved by antioxidant status alteration. Further clinical and experimental studies are needed for better understanding of oxidative stress mechanism and the impact of antioxidant supplementation on reproduction.

INTRODUCTION

Gestation is characterized by dynamic changes in several organs that lead to increased basal oxygen consumption and modifications in both maternal and fetal. Early gestation corresponds to the maternal anabolic state with an increase in adipose tissue and insulin sensitivity. Nutrients are stored in early gestation to meet the feto-placental and maternal demands of the end of gestation and beginning of lactation. In contrast, the end of gestation corresponds to a catabolic state with decreased insulin sensitivity and enhanced insulin resistance, which results in increased maternal glucose and free fatty acids concentrations, allowing greater availability of substrate for fetal growth[1] (LAIN, 2007).

There is evidence that gestation is a state of high oxidative stress, both in animals[2] (MARTINS

& COSTA, 2008) and in humans.[3] (GRUPTA, et al 2005) Oxidative stress corresponds to event resulting from an imbalance between the production of reactive species (oxygen, ROS, and nitrogen, RNS) and antioxidant capacity. Regarding its high ability to oxidize important cellular components (lipids, proteins, and deoxyribonucleic acid - DNA), oxidative stress is now recognized as one of the most common mechanisms involved in the development of a variety of diseases[4] (HALLIWELL & GUTTERIDGE,1999) as well as natural events, such as gestation[5,6] (SPEAKMAN, 2008; ALONSO-ALVAREZ, et al 2004).There are several factors triggering oxidative stress during gestation. The placenta has a major influence on fetal homeostasis. Rich in mitochondria, the placenta consumes 1% of the maternal basal metabolic rate when fully developed[7] (Sies, 1991). In parallel to the increase in metabolic rate, there is an enhance in maternal minute ventilation (35-50%) to achieve the requirement of maternal and fetal oxygen[8,9,10] (CLAPP, et al 1988; PERNOLL, 1975; ALAILY & CARROL, 1978). Furthermore, the high metabolic demand due to higher need of tissue irrigation and oxygenation, may favor the increased generation of ROS[11] (GITTO, et al 2009). This highly aerobic environment is probably responsible for the augmented oxidative stress in gestation.

Throughout gestation lipid peroxides are formed and transported to other parts of the body by lipoproteins. Thus, damage occurs not only at the site where the reactive species is formed, but also at distance. This transport therefore promotes dissemination of lipid peroxide, which features an amplification and perpetuation of oxidative injury.[3]

It has also been suggested an increased inflammatory status during gestation, which increases susceptibility to ROS generation[12] (KONTIC-VUCINIC, et al 2008). ROS and RNS associated with inflammation are also known to cause damage to DNA. In addition, the DNA ability to repair itself is reduced in pregnant women, which makes them more vulnerable to environmental and endogenous toxins that can lead to diseases[13] (SKONER, et al 1995).

Gestation per se is susceptible to oxidative stress and antioxidant defenses may be altered in response to elevated levels of reactive oxygen species,[14] (CHEN & SCHOLL, 2005) in animals[2] (MARTINS & COSTA, 2008) and also in humans[3] (GRUPTA, et al 2005). However, this increase does not necessarily lead to a prolonged oxidative stress[5] (SPEAKMAN, 2008)due to a number of defense mechanisms that repair damage and limit new occurrences[15,16] (VASILAKI, et al 2006; VALKO, et al 2007).

ANTIOXIDANT DEFENSE STATUS

Studies that examine the antioxidant defense system have shown controversial results. Progressive enhance in enzymatic (SOD, catalase, glutathione peroxidase) and non-enzymatic (glutathione, bilirubin) antioxidant defense systems have been showed in placental homogenates and syncytiotrophoblastic brush border at early, mid gestation and at term[17,18,19] (QANUNGO, et al 2000; WATSON, et al 1998; WATSON, et al 1997). Glutathione peroxidase in red bood cells and platelets and extra cellular SOD activity has also been reported to be increased[20,21] (UOTILA, et al 1991; TAMURA, et al 2001). On the other hand, the hydrophilic antioxidant capacity was declined in plasma from healthy pregnant women when compared to non-pregnant women[22](ADIGA & ADIGA, 2009). It has been identified that the ability of hydrophilic[23](TOESCU, et al 2002) and lipophilic[24,25] (WANG, et al 1991; DE VRIESI, et al 2001) antioxidant defense system are progressively reduced during gestation. Studies in rats have shown that females use mechanisms to deal with the consequences of increased energy demands[26] (GARRATT, et al 2011),such as, the increase in antioxidant defense expression genes[27] (JONES, et al 2011). Examining cows in lactation, it has been shown that efficiency in antioxidant defenses is able to keep oxidative homeostasis, despite the increased oxidative phenomenon under the influence hormonal and metabolic[28] (PICCIONE, et al 2007). On the other hand, we recently identified that sows are under high systemic oxidative stress, especially at the end of gestation and during lactation compared to early gestation, and not fully recovered until the weaning period[29] (BERCHIERI-RONCHI, et al 2011).

PREGNANCY COMPLICATIONS

Oxidative stress is also an event related to complications of pregnancy. In fact, the mechanism of pregnancy interruption[3,30] (GRUPTA, et al 2005; AGARWAL, et al 2006), pre-eclampsia and intrauterine growth restriction[3](GRUPTA, et al 2005) has been associated with oxidative stress in various animal species. A recent study showed decreased

glutathione peroxidase activity was associated with a reduction of selenium in pregnant women who have suffered abortion or pre-eclampsia[31] (MISTRY & WILLIAMS, 2011).

LACTATION

There is evidence of the presence of antioxidant agents in colostrum and milk in cows[32] (LINDMARK-MANSSON & AKESSON, 2000). Data obtained from bovine colostrum and milk showed dynamic changes in total antioxidant capacity within seven days postpartum[33] (KANKOFER & LIPKO-PRZYBYLSKA, 2008). Study in pigs showed that milk provides a higher concentration of antioxidants between the second to fifth lactation, offering best defense against ROS for mammary glands and newborns[34] (LIPKO-PRZYBYLSKA & KANKOFER, 2012). Examining coenzyme Q10 concentration, previous report identified its highest breast milk concentration from mothers of full-term infants, which decreasing during lactation. In addition, coenzyme Q10 and α and γ-tocopherol concentration was directly correlated with the antioxidant capacity in human milk 35 (QUILES, et al 2006).

Examining a mice lactation, a recent study showed absence of differences in lipid peroxidation (malondialdehyde: liver, gastrocnemius muscle and serum) and antioxidant system (total glutathione, protein thiol content, oxidized glutathione) between virgin females, primiparous females at peak lactation, and primiparous females after their first litter was fully weaned.[26] Other reported more lipid peroxidation and low glutathione in plasma from dairy cows in early gestation as compared to those of advanced pregnant[36] (SHARMA, et al 2011).

NEONATES

Newborns may also suffer oxidative stress interference. Although, study has identified a low oxidative stress associated with abundant vitamin C at birth[37] (UPHADYAYA, et al 2005), clinical study found oxidative DNA damage in mononuclear cells from umbilical cord blood, as well as other redox state index, suggesting that a sudden increase in oxygenation may exposes the newborn to oxidative stress[38] (ZHAO, et al 2004). Due to that, it has been suggested that providing the baby amino acid substrates for cellular glutathione synthesis immediately after birth promotes antioxidant defense improvement at the early stages of life. Breast milk has been found to have many advantages over formula, including the potential to provide antioxidant protection to infants[39] (PERRONE, et al 2007).

ANTIOXIDANT SUPPLEMENTATION

Studies that examined the antioxidant supplementation have shown controversial results. Using an experimental model in pigs, previous study showed that dietary supplementation with α-tocopherol during gestation resulted in an increase of its concentration in colostrum, milk, tissues and plasma from the creates at weaning. In the same study it was further shown that the combination of α-tocopherol and dietary vitamin C increased concentration of total immunoglobulins and IgG in plasma from the creates[40] (PINELLI-SAAVEDRA, et al 2008). Review by Pinelli-Saavedra (2003) 41 (PINELLI-SAAVEDRA, 2003) suggests that dietary supplementation or injection of vitamin E with selenium in sows had a positive effect on reproductive performance than vitamin E administered alone. Examining a physiological gestational model in Wistarrats, our group recently showed that tomato oleoresin supplementation during gestation was accompanied by a significant reduction in oxidative damage of purine and pyrimidine bases in DNA from peripheral lymphocytes at the end pregnancy as compared to those of pre-mating[42] (BERCHIERI-RONCHI, 2013). On the other hand, an experimental study observed that supplementation with G.bilobaextract in pregnant diabetic mice alters neither antioxidant parameters in dam and breed nor reproductive performance and perinatal outcomes[43] (POSTON, et al 2006).Recent clinical study showed that dietary deficiency of vitamins A and E during lactation mother was correlated with low levels of these vitamins in breast milk 44 (DUDA, et al 2009). Similarly, maternal inadequate dietary intake of vitamin A and selenium during lactation significantly decreased the concentration of these nutrients in milk[39] (PERRONE, et al 2007). Clinical studies have reported the antioxidant supplement on pre-eclampsia. Early supplementation with low micronutrient levels of antioxidants during women gestation may reduce the disease risk[45] (WIBOWO, et al 2005). Treatment with the combination of antioxidants and various nutrients (n-acetylcysteine, selenium, zinc, copper, manganese, iron, B complex, folic acid, calcium and vitamin A, C, E) was associated with better outcomes of both maternal and perinatal pregnant women with deficient antioxidant defense when compared to control. Furthermore, pre-eclampsia was significantly less frequent in women

that received the supplementation as compared to those of control group[44] (DUDA, et al 2009). Ashok et al.46 (2011) showed that lycopene supplementation does not prevent pre-eclampsia in women although may reduce fetal complications.[46] (ANTARTANI & ASHOK, 2011) Systematic reviews also have shown absence of evidence of antioxidant supplementation use on pre-eclampsia. Combined vitamin C and E supplementation during gestation did not prevent the risk of pre-eclampsia and other events (fetal or neonatal loss, low birth weight for gestational age or premature birth).[47] (POLYZOS, et al 2007) Recent study did not support the use of antioxidants during gestation for the prevention of low, moderate, or high risk of pre-eclampsia other outcomes[48] (SALLES, et al 2012). Examining 10 trials (6533 women), other found no reduction in pre-eclampsia, high blood pressure or preterm birth with the use of antioxidant supplements. When antioxidants were assessed separately, there were insufficient data to be clear about whether there was any benefit or not, except for vitamin C and E. The authors conclude that the study does not support the use of antioxidants to reduce the risk of pre-eclampsia or other complications in gestation[49] (RUMBOLD, et al 2008).

It may be considered that the actions of antioxidants in biological systems depend on the nature of oxidants or ROS/RNS imposed on the systems. Besides, the activities and amounts of antioxidants present and their cooperative/ synergistic interactions in these systems interfere in the antioxidant function. High doses of a single or limited mixture of antioxidant supplements may not affect the already saturated in vivo antioxidant network, but rather could result in an imbalance in the antioxidant network and could possibly even act as pro-oxidants[50] (YEUM, et al 2010).

Although oxidative stress is an important mechanism in reproduction process, there are insufficient data to make a recommendation regarding antioxidant supplementation alone, or in combination with other antioxidants. Indiscriminate use of antioxidant supplements should be discouraged due to the undesirable pro-oxidant phenomenon. The beneficial action of a particular antioxidant is the result of a delicate synergism between antioxidants present in the lipophilic and hydrophilic compartments. Thus, a single antioxidant supplementation may trigger irreversible commitment of all antioxidant defense system. Further studies, both experimental as well as clinical trials are needed for better comprehension.

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Correspondingauthor:
Dr. Ana Lucia Anjos Ferreira
Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, UNESP
CEP 18618-970, Botucatu, SP, Brasil
Phone/FAX: +55-14-38801171 / +55-14-38822238
ferreira@fmb.unesp.br