Journal of Natural Sciences Research www.iiste.org
ISSN 2224-3186 (Paper) ISSN 2225-0921 (Online)
Vol.3, No.13, 2013

The Developmental and Physiological Interactions between Free Radicals and Antioxidant Defense System: Effect of Environmental Pollutants

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Abstract
This review explores the relation between antioxidant defense system and reactive oxygen species (ROS) during the development and shows the effect of environmental pollutants on this process. In normal state, the decline in levels of free radicals is coupled with increased antioxidant and the reverse is true, but there is a critical balance between them during the development. Also, redox signaling induced by environmental pollutants (stressors) involves both alterations in antioxidant defenses and accumulation of ROS leading to oxidative stress which acts as a critical pathophysiological mechanism. This disturbance has deleterious effect on male/female reproductive functions, on the development of the blastocysts and on the health of the embryos, newborns (perinatal life) and adulthood. Also, this overview shows that sperm, egg, zygote or blastocyst derived during the abnormal production of ROS due to environmental pollutants may result into offspring with high risk of any type of diseases producing developmental delay, embryopathy, teratogenic changes and apoptosis. These early insults may then lead to an increased rate of miscarriage and congenital anomalies depending on free radicals signaling and cell-death pathways. Thus, maintaining the balance between antioxidants and ROS during pregnancy or lactation period may modulate normal fetal/neonates growth and development, and may play an important role in a healthy life for the newborns. However, this argument is still ambiguous because of the difficulties of to what degree oxidants could participate as signaling molecules controlling fundamental and developmentally relevant cellular processes such as proliferation, differentiation, and death.
Keywords: Antioxidants, Reactive Oxygen Species, Development, Environmental Pollutants.

1. Introduction

In mammalian cells, antioxidant defenses consist of enzymatic antioxidants [superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST) and catalase (CAT) (Ames 1993; Piper 1995; Sardesai 1995; Betteridge 2000; Ahmed 2005 & 2012a; Ferrari *et al.* 2009; Makker *et al.* 2009; Matés *et al.* 2010; Garrel *et al.* 2010; Jain *et al.* 2011; Ahmed *et al.* 2012; Rahman 2012; Al-azzawie *et al.* 2013; Imosemi 2013) and non-enzymatic antioxidants [ascorbic acid (vitamin C), α-tocopherol (vitamin E), total thiol (t-SH), glutathione (GSH), carotenoids, flavonoids, and other antioxidants (Valko *et al.* 2007; Ahmed 2012a; Ahmed *et al*. 2012; Lombardo *et al*. 2013; Neeraj *et al.* 2013; Rossi *et al*. 2013)]. Specifically, enzymatic defenses are responsible for the scavenging of ROS, reactive nitrogen species (RNS), and their intermediates (Mruk *et al.* 2002; Ferrari *et al.* 2009; Makker *et al.* 2009; Garrel *et al.* 2010; Ziech *et al.* 2010; Ahmed 2012a; Ahmed *et al.* 2012; Petrulea *et al.* 2012; Rahman 2012; Kalyanaraman *et al.* 2012; Al-azzawie *et al.* 2013; El-Bahr 2013; Imosemi 2013; Neeraj *et al.* 2013; Poljšak and Milisav 2013).

Life on earth depends upon oxygen as the final acceptor of electrons in mitochondrial electron transport (Phillips 2003), but the process also generates toxic metabolites (Ahmed 2012a; Ahmed *et al*. 2012; Al-azzawie *et al.* 2013). ROS leak from mitochondria into the cytoplasm and nucleus where they cause cellular damage by oxidizing DNA, proteins, lipids, and carbohydrates (Mena *et al.* 2009; Garrel *et al.* 2010; Jain *et al.* 2011; Lushchak 2011; Small *et al.* 2012; El-Bahr 2013; Treidel *et al.* 2013). However, ROS/RNS are known to act as secondary messengers controlling normal physiological functions of the organism and therefore the production of nitric oxide ($NO^{\bullet}$) by nitric oxide synthase (NOS) and superoxide by nicotinamide adenine dinucleotide (phosphate) hydrogen (NAD(P)H) oxidase is tightly regulated by hormones, cytokines, and other mechanisms (Dröge 2002; Incerpi *et al.* 2007; Valko *et al.* 2007; De Vito *et al*. 2010 & 2013). This regulation involves signal transduction pathways regulating gene expression, cell replication, differentiation, and apoptotic cell death (Sen & Packer 1996; Suzuki *et al.* 1997; Finkel 1998; Andrieu-Abadie *et al.* 2001; Mena *et al.* 2009; Garrel *et al.* 2010; Lushchak 2011; Ahmed *et al*. 2012; Roopha & Latha 2013). In general, oxidative stress (OS) can be caused by excessive stimulation of NAD(P)H by cytokines, or by the mitochondrial electron transport chain and xanthine oxidase (Rizzo *et al.* 2007).

Many molecules relevant for development are sensitive to the action of ROS (Kheirat *et al.* 2013). Al-Gubory *et al.* (2010) recorded that ROS and antioxidants have been implicated in the regulation of reproductive processes (cyclic luteal and endometrial changes, follicular development, ovulation, fertilization, embryogenesis, embryonic implantation, and placental differentiation and growth) in both animal and human. Imbalances between ROS production and antioxidant systems induce OS that negatively impacts reproductive processes. Interestingly, the amount of ROS produced by embryos varies with the stage of development (Nasr-Esfahani *et al.* 1991; Favetta *et al.* 2007; Ahmed 2012a; Ahmed *et al*. 2012; Roopha & Latha 2013) and increases when embryos are produced *in vitro* compared to those derived *in vivo* (Goto *et al.* 1993). Moreover, Saker *et al.* (2008) and Ahmed (2012a) hypothesized that high levels of ROS during embryonic, fetal and placental development are a feature of pregnancy. In addition, oxygen radicals together with nitric oxide may regulate the circulation, energy metabolism, and the reproduction and remodelling of cells during the embryonic development (Rizzo *et al.* 2007; Ufer & Wang 2011; Ahmed 2012a; Ahmed *et al*. 2012).

However, how ROS may affect growth and differentiation of mammalian cell? Another question is how to protect the embryo from free radical damage, as exposure of early embryos to environmental oxygen concentrations? The answer to these questions is not known but some observations suggest that it is possible. Thus, we here review some of the interesting features about the interactions between antioxidants and ROS during development in different mammalian animal or species. We first present a concise introduction on ROS, antioxidants and then on different developmental periods, pregnancy outcomes and show the effect of different environmental pollutants to enable the reader to follow what is presently known on the interactions between them. There is a significant body of literature on some of the aspects considered in this review, but we will rather select reviews and more relevant articles when reporting on subjects not directly related to the main topic.

2. Oxidative Stress

OS is an imbalance between oxidants and antioxidants resulting from increased generation of oxidants and/or reduction in the amounts of antioxidants (Ahmed 2005; Ma 2009; Limón-Pacheco & Gonsebat 2009; Makker *et al.* 2009; Mena *et al.* 2009; Ahmed *et al*. 2012; Petrulea *et al.* 2012; Al-azzawie *et al.* 2013; Poljšak and Milisav 2013). OS includes a broad diversity of physiological and pathophysiological, endogenous and exogenous processes that affect the cellular oxidant/antioxidant balance (El-Bahr 2013; Treidel *et al.* 2013). We can take as an example the case of metal-induced oxidative damage (Limón-Pacheco & Gonsebat 2009; Ma 2009; Ahmed 2012a; Ahmed *et al*. 2012). Toxic metals, such as cadmium and chromium, induce OS in a variety of target cells via numerous actions that include directly damaging mitochondrial respiration, increased ROS generation via the Fenton reaction, lipid peroxidation (LPO), and reduction of intracellular antioxidants, such as GSH (Kasprzak 2002; Valko *et al.* 2005; He *et al.* 2007 & 2008; Ahmed 2012a,b). Several investigators (Mena *et al.* 2009; Lushchak 2011; Ahmed 2012a; Al-azzawie *et al.* 2013) undertook that OS within a physiological range is necessary for proliferative stimulation and perhaps the removal of aged cellular components while extensive OS damages the structure and function of tissues. Consequences of OS consist of modifications of cellular proteins, lipids, and DNA (Ahmed *et al*. 2012; Al-azzawie *et al.* 2013; Treidel *et al.* 2013). Modification of proteins, in turn, leads to the formation of carbonyl derivatives by direct oxidation of certain amino acid side chains and oxidation-induced peptide cleavage (Stadtman 1992), as well as modification of lipids leading to LPO (Mena *et al.* 2009; Ahmed *et al*. 2012; El-Bahr 2013). The hydroxyl radical ($^{\bullet}OH$) is the main player in oxidative DNA damage, changing purine and pyrimidine bases and deoxyribose sugar as well as cleaving the phosphodiester DNA backbone to give rise to DNA strand breaks (Ma 2009). Mitochondrial DNA is more sensitive to OS than nuclear DNA because of its proximity to the main source of ROS and a limited DNA repair capacity. Damaged mitochondria produce more ROS and set in motion a vicious cycle in which increasing DNA damage results in increased ROS production that in turn leads to more DNA damage (Mena *et al.* 2009). This vicious nature of oxidative damage may clarify in part why OS is usually associated with chronic diseases, such as neurodegeneration, chronic inflammatory disorders and various cancers.

3. Reactive Oxygen Species And Reactive Nitrogen Species: An Overview

ROS consist of a multiplicity of oxygen-derived small reactive molecules with diverse structures, including oxygen radicals, such as superoxide ($O_2^{\bullet-}$), $^{\bullet}OH$, peroxyl radical ($RO_2^{\bullet}$), and alkoxyl radical ($RO^{\bullet}$), and certain non radicals that are either oxidizing agents and/or are easily converted into radicals, such as hypochlorous acid ($HOCl^{-}$), ozone (O_3), singlet oxygen ($^1O_2$), and hydrogen peroxide (H_2O_2) (Table 1). Some of these species, such as $O_2^{\bullet-}$ and $^{\bullet}OH$ radicals, are very unstable, whereas others, like H_2O_2, are relatively stable and freely diffusible (Ma 2009; Mena *et al.* 2009; Jain *et al.* 2011; Lushchak, 2011; Ahmed 2012a; Ahmed *et al*. 2012; Won *et al.* 2012; Al-azzawie *et al.* 2013; El-Bahr 2013; Kheirat *et al.* 2013; Treidel *et al.* 2013). $NO^{\bullet}$ and the strong oxidant peroxynitrite anion ($ONOO^{-}$) are known RNS. Wright *et al.* (2010) reported that $NO^{\bullet}$ acts in part by limiting inflammatory cell recruitment in the newborn lung. Furthermore, ROS and RNS play important roles in many

physiological processes, and are not only noxious byproducts of metabolism (Dröge 2002; Incerpi *et al.* 2007). ROS can be produced in several compartments and by multiple enzymes in cells (Ahmed *et al*. 2012; Treidel *et al.* 2013). In fact, most, if not all, enzymes that are capable of metabolizing oxygen are also capable of producing ROS (Ma 2009; Ahmed 2012a,b). Mitochondria consume about 90% of the body's oxygen to produce adenosine triphosphate (ATP) by oxidative phosphorylation. *In vitro* data show that 1–2% of the oxygen molecules consumed are converted to $O_2^{\bullet-}$ in mitochondria (Boveris & Chance 1973; Mena *et al.* 2009). Although *in vivo* rate of mitochondrial superoxide production is probable to be much less than this number, the majority of intracellular ROS can be returned to mitochondria (Staniek & Nohl 2000; St-Pierre *et al.* 2002; Won *et al.* 2012). Oxidative phosphorylation in mitochondria utilizes controlled oxidation of nicotinamide adenine dinucleotide hydrogen (NADH) to produce a potential energy from proton gradient across the mitochondrial inner membrane. The energy is then used to phosphorylate adenosine diphosphate (ADP) to ATP. Electrons resulting from NADH, along the respiratory chain, can directly react with oxygen and produce free radicals (Ma 2009). Productions of $O_2^{\bullet-}$ in mitochondria detected mainly in complex I (NADH dehydrogenase) and complex III (ubiquinone cytochrome c reductase), with the latter being the main site of ROS generation under normal metabolic events (Turrens 1997; Mena *et al.* 2009; Won *et al.* 2012).

Other enzymes related to OS are the expanding family of ROS-producing NADPH oxidases (NOXs), such as NOX1, NOX2, NOX3, NOX4, NOX5, and thyroid oxidases (DUOX1 and DUOX2) (Bedard & Krause 2007). Furthermore, Ma (2009) reported that NOX2 (gp91phox) is the prototype of NOX enzymes and is present mostly in neutrophils and other phagocytic cells. $O_2^{\bullet-}$ produced by NOX2 are critical in defense against microbes. Baehner & Nathan (1967) speculated that loss of the function of the NOX2 system is critical for chronic granulomatous disease, a human genetic disorder characterized by decreased bactericidal capability of phagocytes. Non-phagocytic NOXs produce $O_2^{\bullet-}$ and other radicals that may activate the cellular transformation or replicative senescence (Bedard & Krause 2007). These observations support the concept that, in addition to stochastically damaging macromolecules, ROS are used in normal cellular signaling and homeostasis (Mena *et al.* 2009). Additional sources of cytoplasmic ROS generation include cytochrome P450s, lipoxygenases, and one-electron reduction of quinones by NADPH: cytochrome P450 reductase. In this latter case, semiquinone radicals ($Q^{\bullet-}$) generated by enzymatic one-electron reduction cycle back to quinones and, at the same time, pass electrons to O_2 leading to the formation of $O_2^{\bullet-}$ radical. This futile cycling between quinone and semiquinone radical with concomitant generation of ROS contribute to the toxicities of several chemicals that have quinone moieties, such as doxorubicin and menadione (Enster1986; O'Brien 1991). Generally, ROS can be inactivated by other enzymes such as xanthine oxidase, cyclo-oxygenases, and lipoxygenases, CAT, SOD, GPx, but also other molecules may act as ROS scavenger such as peroxiredoxin (Prx) and thioredoxin (Trx).

4. Antioxidant Defense System: An Overview

The cellular redox status and antioxidant defense mechanisms are more sensitive and lower in the embryo compared to adults (Wells *et al.* 2009; Badham &Winn 2010; Davis & Auten 2010; Garrel *et al.* 2010; Ahmed *et al*. 2012; Imosemi 2013). Antioxidant defense mechanisms against free radical-induced oxidative damage include the following (Table 2): **(i)** catalytic removal of free radicals and reactive species by factors such as CAT, SOD, peroxidase and thiol-specific antioxidants; **(ii)** binding of proteins (e.g., transferrin, metallothionein, haptoglobins, caeruloplasmin) to pro-oxidant metal ions, such as iron and copper; **(iii)** protection against macromolecular damage by proteins such as stress or heat shock proteins; and **(iv)** reduction of free radicals by electron donors, such as GSH, vitamin E, vitamin C, bilirubin and uric acid (Halliwell & Gutteridge 1999; Ferrari *et al.* 2009; Garrel *et al.* 2010; Matés *et al.* 2010; Halliwell 2011; Ahmed 2012a; Ahmed *et al*. 2012; Rahman 2012). CATs, in animals, are heme-containing enzymes that convert H_2O_2 to water and O_2, and they are largely localized in subcellular organelles such as peroxisomes (Limón-Pacheco & Gonsebatt 2009; Ferrari *et al.* 2009; Ahmed *et al*. 2012). Mitochondria and the endoplasmic reticulum have little amount of CAT, thus, intracellular H_2O_2 cannot be eliminated unless it diffuses to the peroxisomes (Halliwell & Gutteridge 1999; Ahmed 2005; Halliwell 2011). On the other hand, several investigators (Biswas *et al.* 2009; Ferrari *et al.* 2009; Ahmed *et al*. 2012; Imosemi 2013; Neeraj *et al.* 2013) reported that GPx can remove H_2O_2 by coupling its reduction with the oxidation of GSH and it can also reduce other peroxides, such as fatty acid hydroperoxides. Limón-Pacheco & Gonsebatt (2009) detected these enzymes in the cytoplasm at millimolar concentrations and also in the mitochondrial matrix. Also, Kim *et al.* (2011) reported that SODs are metal-containing proteins that catalyze the scavenging of superoxide anion, generating hydrogen peroxide as a final product of the dismutation. Two SOD enzymes are found in the cell: SOD1 (Cu/ZnSOD) is a copper- and zinc-containing enzyme primarily localized in the cytoplasm and SOD2 (MnSOD) is a manganese-dependent enzyme in the mitochondrial matrix (Ahmed, 2005). SOD catalyzes the conversion of $O_2^{\bullet-}$ to H_2O_2, whereas CAT and GPx convert H_2O_2 to H_2O (Ma 2009; Ahmed *et al*. 2012). In addition, there is a new family of peroxide scavengers termed Prxs (Chae *et al.* 1999). Prxs can reduce peroxides in the presence of Trxs (Ahmed *et al.* 2006). Myeloperoxidase is present in the

granules of neutrophils and catalyzes the conversion of H_2O_2 and Cl^- to more reactive $HOCl^-$, which is critical for the bactericidal activity of neutrophils (Ma 2009). Importantly, Zhuang *et al.* (2010) hypothesized that Heme oxygenase (HO-1) is required for mouse postnatal lung alveolar development and that vascular expression of HO-1 is essential and protective during postnatal alveolar development.

Table 1. Overview about the molecules mediating oxidative stress and cell damage.

Name	Structure	Main reactions	Cell components attacked by ROS	References
Superoxide	$^{\bullet}O–O^-$	Catalysis of Haber–Weiß reaction by recycling ferrous and copper ions; formation of H_2O_2 or peroxynitrite.	Lipids: peroxidation of unsaturated fatty acids in cell membranes. - Oxidizing DNA or proteins.	Sies (1997), Sorg (2004), Ahmed (2012a) and Won *et al.* (2012)
Singlet oxygen	O=O	Reaction with double bonds, formation of peroxides; decomposition of amino acids and nucleotides.	Nucleic acids: base hydroxylation, cross-linkage, DNA strand scission.	Sorg (2004) and Mena *et al.* (2009)
Ozone	$^-O–O^+=O$	Oxidation of all kinds of biomolecules, especially those containing double bonds; formation of ozonides and cytotoxic aldehydes.	Oxidation of proteins, membrane lipids and DNA.	Löffler & Petrides (1988), Kanofsky (1989), Halliwell & Gutteridge (1999), Mathews-Roth (2000) and Halliwell (2011)
Hydroxyl radical	$^{\bullet}OH$	Hydrogen abstraction; production of free radicals and lipid peroxides; oxidation of thiols.	Inhibition of protein, nucleotide, fatty acid biosynthesis.	Taira *et al.* (1992) and Tyrrell (1995)
Hydrogen peroxide	HO–OH	Formation of $^{\bullet}OH$; enzyme inactivation; oxidation of biomolecules.	Proteins oxidation of sulfhydryl-containing enzymes (enzymes inactivation, DNA oxidation or LPO.	Sies (1997), Halliwell & Gutteridge (1999) and Halliwell (2011)
Nitric oxide	$^{\bullet}N=O$	Formation of peroxynitrite; reaction with other radicals.	Lipid, protein and DNA oxidation.	Dawson & Dawson (1996) and Halliwell & Gutteridge (1999)
Peroxynitrite	$O=N–O–O^-$	Formation of $^{\bullet}OH$; oxidation of thiols and aromatic groups; conversion of xanthine dehydrogenase to xanthine oxidase; oxidation of biomolecules.	Membrane-LPO, DNA damage and apoptosis and protein oxidation.	Pryor & Squadrito (1995), Squadrito & Pryor (1995) and Halliwell & Gutteridge (1999)
Hypochlorite	ClO^-	Oxidation of amino and sulphur-containing groups; formation of chlorine.	LPO, or oxidizing DNA or proteins.	Sies (1997), Halliwell & Gutteridge (1999), Klebanoff (1999) and Winterbourn *et al.* (2000)
Peroxyl radical	$R–O–O^{\bullet}$	Hydrogen abstraction; formation of radicals; decomposition of lipids and other biomolecules.	Carbohydrates depolymerization of polysaccharides.	Sorg (2004) and Ahmed (2005)
Hydroperoxide	R–O–OH	Oxidation of biomolecules; disruption of biological membranes.	Oxidation of proteins, membrane lipids and DNA by the peroxide ions.	Löffler & Petrides (1988) and Sorg (2004)
Copper and iron ions	Cu^{2+}, Fe^{3+}	Formation of $^{\bullet}OH$ by Fenton and Haber–Weiß reactions.	LPO, or oxidizing DNA or proteins.	Sies (1997) and Sorg (2004)

Table 2. Overview of endogenous antioxidants (Sorg 2004).

Antioxidant	Phase	Action
SOD	Hydrophilic	- Dismutation of O_2^- into H_2O_2 and O_2.
CAT	Hydrophilic	- Dismutation of H_2O_2 into H_2O and O_2.
GPx	Hydrophilic or lipophilic	- Reduction of R–OOH into R–OH.
GR	Hydrophilic	- Reduction of oxidized glutathione (GSSG).
GST	Hydrophilic	- Conjugation of R–OOH to GSH (→GS–OR).
Metallothioneins	Hydrophilic	- Binding to transition metals (= neutralisation).
Trxs	Hydrophilic	- Reduction of dithio acid (R-S-S-R) into thiol acid (R-SH).
GSH	Hydrophilic	- Reduction of R–S–S–R into R–SH. - Free radical scavenger. - Cofactor of GPx and GST.
Ubiquinol	Lipophilic	- Free radical scavenger (prevents LPO).
(Dihydro)lipoic acid	Amphiphilic	- ROS scavenger. - Increases antioxidant and phase II enzymes.
Ascorbic acid	Hydrophilic	-Free radical scavenger. -Recycles vitamin E. -Maintains enzymes in their reduced state.
Retinoids (vitamin A) and carotenoids	Lipophilic	-Free radical scavengers. - $^1O_2$ quencher.
Tocopherols	Lipophilic	-Free radical scavenger (prevents LPO). -Increases selenium absorption.
Selenium	Amphiphilic	- Constituent of GPx and Trxs.

On the other hand, nonenzymatic antioxidant molecules include vitamin E, vitamin A, vitamin C, GSH, estrogens, creatine (a nitrogenous compound), xanthophylls (yellow pigments related to carotene), flavonoids (aromatic oxygen heterocyclic compounds that are widely distributed in higher plants) (Rossi *et al*. 2013; Lombardo *et al.* 2013), metallothionein (cadmium-binding protein involved in heavy metal detoxification), taurine (an aminosulfonic acid) and its precursors, and other thiols, such as nonstructural polyunsaturated lipids (Van Poppel & van den Berg 1997; Lee 1999; Ahmed 2012a). For instance, lipid-soluble vitamin E and carotene may inhibit the oxidation of low-density lipoprotein (LDL) (Li *et al.* 1996), which can lead to cardiovascular diseases, atherosclerosis and cancer (Traber & Packer 1995). Vitamin E has also been shown to regulate signal transduction actions (Brigelius-Flohe & Traber 1999; Gopalakrishna & Jaken 2000; Ahmed 2012a), and contribute to spermatogenesis (Bensoussan *et al.* 1998). Bensoussan *et al.* (1998) speculated that vitamin E-deficient rats exhibited abnormal spermatogenesis with spermatids being the most advanced cell type presents. Generally, the antioxidants play an important role in the development of most biological systems, particularly cerebellum (Ahmed *et al.* 2012; Imosemi 2013) and cerebrum (Ahmed *et al.* 2012). However, the mechanism(s) by which other antioxidant molecules function in protecting cells from ROS- and RNS-induced damage is not completely recognized. Thus, the normal expressions and maturations of several antioxidant systems were summarized in table 3.

Table 3. Maturation of antioxidant system

Expression of antioxidants	Species	References
- The antioxidant defense mechanism is gradually developing with the advancement of pregnancy.	Rat	Zaken *et al.* (2000) and Ornoy *et al.* (2009)
- An abrupt drop in SOD activity at the perihatching stage.	Chick	Thomas *et al.* (1997)
- Marked expression vitamin E in the development of placental labyrinth trophoblast (throughout pregnancy).	Human	Jishage *et al.* (2001)
- Total antioxidant activity and CAT activity peaked in the brain, liver, heart muscle, skeletal muscle, kidneys, and blood serum at days 14 - 30 of development.	Rat newborns	L'vova & Abaeva (1996)
- Total SOD decreased on day 6, increased again on 10 day old, and remained constant thereafter. - Cu/ZnSOD levels were low at birth and reached adult levels on the 10th day after birth.		Shivakumar *et al.* (1991)

- SOD and Prxs are particularly abundant in oocytes and early embryos.	Human		Guérin *et al.* (2001) and Donnay & Knoops (2007)
- Obvious expression of GSH and its synthesizing enzymes, Cu/ZnSOD, MnSOD, and GPx in the oocyte and early embryo.			Guérin *et al.* (2001)
- Marked expression of GST at very early stages of embryonic development.	Toad		Anguiano (2001)
- Increased GPx in brain during the second half of the in ovo incubation period.	Embryonic chick		Wilson *et al.* (1992)
- Increased GSH during the first divisions of oocyte.	Human		Gardiner & Reed (1994)
- Increased GPx and CAT in liver during the final week before birth.	Both birds and mammals		Rickett & Kelly (1990) and Wilson *et al.* (1992)
- Decreased GPx and CAT in brain from gestation day (GD) 19 into postnatal day (PND) 2.	Rat		Del Maestro & McDonald (1987)
- The specific activity of GPx doubles and that of CAT falls 4-folds in brain during the final 2 weeks in ovo.	Embryonic chick		Wilson *et al.* (1992)
- Obvious expression of Cu/ZnSOD in late gestational and neonatal periods.	Rat		Del Maestro & McDonald (1987)
- Marked expression of MnSOD in embryonic brain.	Chick		Wilson *et al.* (1992)
- SOD is maintained at constant level during days 45-60 of gestation.	Guinea pig		Mishra & Delivoria-Papadropoulos (1988)
- Increased CAT, SOD and GPx during the course of egg and embryonic development.	Prawn *M. malcolmsonii*		Arun & Subramanian (1998)
- Increased SOD and whole body CAT and GPx in embryo.	Turbot *Scophthalmus maximus*		Peters & Livingstone (1996) and Livingstone (2001)
- Increased Cu/ZnSOD and GPx-1.	During pulmonary ontogenesis	Mouse	de Haan *et al.* (1994)
- Increased glucose-6-phosphate dehydrogenase (G6PDH), MnSOD, Cu/ZnSOD, CAT, and GPx.		Rat	Tanswell & Freeman (1984), Hass & Massaro (1987) and Hayashibe *et al.* (1990)
- Increased SOD, CAT, GPx, and decreased Cu/ZnSOD.		Guinea pig	Sosenko & Frank (1987), Rickett & Kelly (1990) and Yuan *et al.* (1996)
- Increased SODs (MnSOD, Cu/ZnSOD).		Human	Autor *et al.* (1976)
- GPx and Cu/Zn SOD are highly expressed in metabolically active tissues during embryogenesis.	Mouse		Baek *et al.* (2005), Schneider *et al.* (2006), Lee *et al.* (2008a) and Yon *et al.* (2008)
- Obvious expression of cytosolic Cu/ZnSOD and of Mn-SOD in germ cells of the testis.	Rat		Bauché *et al.* (1994) and Fujii *et al.* (2003)
- Marked expression of SODs, CAT and GPx in Leydig, peritubular myoid, and Sertoli cells.			Bauché *et al.* (1994) and Luo *et al.* (2006)
	Guinea pig		Kukucka & Misra (1993)
- Obvious expression of ascorbic acid content in the testes during the developmental phases.	human		Mukkadam (1980)
- An increasing trend of α-tocopherol, ascorbic acid, bilirubin, and GSH with gestational progress.	Human placental brush-border membrane (BBM)		Sen & Mukherjea (1998) and Qanungo *et al.* (1999)
- Marked expression of SOD, CAT, GPx and GR in term placental BBM and umbilical cord (UC) blood.	Human		Qanungo *et al.* (1999)
- High plasma ascorbate levels, and low total plasma antioxidant activity in preterm babies.			Gophinathan *et al.* (1994)
- Low GPx expression in erythrocytes of newborns.			Gross *et al.* (1967) and Whaun & Oski (1970)
- Vitamin E deficiency in the cord blood of full term and premature newborns.			Haga & Lunde (1978)
- Low membrane thiol groups in RBCs of the newborn infant.			Schroter & Bodemann (1970)
- Low GSH levels and SOD in erythrocyte of pregnant women at the third trimester.			Nakai *et al.* (2000) and Arikan *et al.* (2001)
- Obvious expression SOD, CAT and GPx in the lungs during late gestation.	Rabbits		Frank & Groseclose (1984)
- Marked expression of extracellular (EC)-SOD primarily intracellular (cytoplasmic) in newborns.	Human		Nozik-Grayck *et al.* (2000) and Auten *et al.* (2006)
- Increased SOD, CAT, GPx, and GR during gestation period.			Qanungo & Mukherjea (2000)
- High concentrations of the antioxidants taurine and vitamins A and E in fluid from the extra-embryonic			Jauniaux *et al.* (2003)

coelum at 5 weeks' gestation.			
- Increase in expression of CAT, Cu/ZnSOD and MnSOD in placental villi at approximately 12 weeks' gestation in tissue obtained prior to pregnancy termination.			Poston & Raijmakers (2004)
- Increased GR, GST, GPx, SOD, CAT, peroxidase (PO), lactoperoxidase (LP), and polyphenol oxidase (PPO).	In different brain regions with the age progress	Rat	L'vova & Abaeva (1996) and Ahmed (2005 & 2012b)
- Increased vitamin C, vitamin E, t-SH, and GSH.			Shivakumar *et al.* (1991) and Ahmed (2005 & 2012b)
- Increased GR, GST, GPx, SOD, CAT, PO, LP and PPO.		Mice	Hussain *et al.* (1995)
- Increased vitamin C, vitamin E, t-SH and GSH.			
- Fall in MnSOD activity in liver during the first week after hatching.	Chick		DeRosa *et al.* (1980) and Ahmed (2005)
- Obvious expression of GSH in early embryos.	Toad		Betteridge (2000) and Ahmed (2005)
- Marked expression of taurine and hypotaurine in the oviductal fluid.	Sow, goat, rabbit and cow		Lonergan *et al.* (1999)
- Taurine is a major component of the free amino acid pool.	In oviductal fluid	Murine	Dumoulin *et al.* (1992)
	In uterine fluid	Rabbit	Miller & Schultz (1987)
	In oocytes	Murine and rabbit	Schultz *et al.* (1981) and Miller & Schultz (1987)

5. Role Of ROS In Development

There is a clear balance between the functions of ROS and antioxidants to maintain homeostasis throughout development (Covarrubias *et al.* 2008; Ahmed 2012a; Ahmed *et al*. 2012; Kheirat *et al.* 2013). Moreover, Dennery (2010) reported that the disturbance in this balance leads to abnormalities that can have an impact on germ cells, the embryo, and the fetus and can have long-term consequences on the mature organism, depending on the timing of these conditions. Germ cells are particularly sensitive to changes in OS because of the high concentration of polyunsaturated fatty acids in sperm cells makes them highly susceptible to ROS (Kim & Parthasarathy 1998). Interestingly, OS affects multiple physiological processes, from oocyte maturation to fertilization, embryo development and pregnancy (Agarwal *et al.* 2006; Roopha & Latha 2013). Furthermore, human sperm is capable of producing low levels of H_2O_2 and $O_2^{\bullet -}$, which are critical factors to the capacitation process that allows the sperm to penetrate the zona pellucida of the ovum (Kim & Parthasarathy 1998). However, spermatozoa possess little capability to protect themselves against OS and they are susceptible to oxidative DNA damage (Aitken & Baker 2006). Several authors (Mena *et al.* 2009; Dennery 2010; Won *et al.* 2012) reported that the DNA damage occurs at both the mitochondrial and the nuclear levels, thereby impairing mitochondrial biogenesis and changing protein synthesis. This leads to proliferation-impaired embryonic development and/or increased morbidity in the offspring (Baker & Aitken 2005; Ahmed *et al*. 2012; Kheirat *et al.* 2013). When the uteroplacental circulation has been established and the placenta has become the source of nutrition and respiratory exchange, the embryo can better withstand OS because its antioxidant defenses are enhanced (Burton 2009). The level of programmed oxidative tone (redox switching) may change the fate of cells in the embryo toward proliferation, differentiation, apoptosis, or necrosis (Dennery 2010; Ahmed 2012a). A much reduced state results in proliferation, mild oxidation state leads to differentiation and further oxidation state causes cell death (Schafer & Buettner 2001; Lushchak 2011; Ahmed *et al*. 2012). Last, neuronal death, in a chick embryo model, was prevented by antioxidants, but their excessive levels were equally detrimental, suggesting that there is a set point for redox status at vital periods of development and that reductive stress is just as dangerous as OS (Castagne *et al.* 1999). The level of oxygen can also affect the differentiation and growth of the stem cells to a particular phenotype (Powers *et al.* 2008). This is mainly critical in the proliferation of pancreatic β cells, for example (Simmons 2006; Kheirat *et al.* 2013). Overall, these findings have important implications for the developing organism as they revealed that the level of oxidant stress and ROS can deeply influence development (Table 4).

Table 4. The interactions between the reactive oxygen species and development.

Remarks	Functions	Species	References
Presence of $NO^{\bullet}$	It is responsible for the regulation process of the sperm capacitation process.	Mouse	Herrero *et al.* (1997)
Blastocoel fluid contains amounts of H_2O_2 toxic to malignant pretrophectodermal cells.	It is important to the regulation process of blastocyst tissue mass by apoptosis.		Pierce et al. (1991)
Increased $^{\bullet}O_2^-$ levels in peri-implantation blastocyst.	It is required for the blastocyst hatching process.		Thomas *et al.* (1997)
H_2O_2 stimulates uterine contractions.	It is necessary for the peri-partum regulation of prostaglandin production.	Rat	Cherouny *et al.* (1988)
Increased $^{\bullet}O_2^-$ levels in day-5 uterus pregnancy.	It is responsible for the regulation process of vascular permeability at the initiation of implantation.	Mouse	Laloraya *et al.* (1989a,b)
High levels of $^{\bullet}O_2^-$ exhibit marked changes in the uterus during the oestrous cycle.	It is important to the regulation process of uterine oedema and cell proliferation.	Rat	Laloraya *et al.* (1991)
H_2O_2 or $^{\bullet}O_2^-$ reduce oxytocin-induced myometrial contractility.	It is essential to the uterine contraction.	Human	Warren *et al.* (2005)
Increased placenta tumor necrosis factor-α (TNF-α) levels.	It causes preeclampsia.		Wang & Walsh (1996)
Increased plasma leptin levels and placenta leptin mRNA.			Mise *et al.* (1998)
Increased placenta 8-isoprostane levels.			Walsh *et al.* (2000)
Increased placenta $^{\bullet}O_2^-$ concentrations.			Sikkema *et al.* (2001)
Increased placental and decidual protein carbonyl (PCa).			Zusterzeel *et al.* (2001)
Increased plasma PCa and H_2O_2 levels.			Tsukimori *et al.* (2008)
Increased serum and term placenta H_2O_2 levels.			Aris *et al.* (2009)
Increased plasma, UC blood and placental malondialdehyde (MDA) levels.	It causes intra-uterine growth restriction (IUGR).		Biri *et al.* (2007)
Increased serum MDA and 4-hydroxyalkenals concentrations.			Karowicz-Bilinska *et al.* (2007)
Increased plasma ROOH and PCa levels.			Saker *et al.* (2008)
Increased platelet $ONOO^-$ level			Nanetti *et al.* (2008)

6. Summary About The Effect Of Antioxidant System On Different Developmental Stages (Table 5).

Table 5. The interactions between the antioxidant system and development.

Remarks	Functions	Species or culture	References
I- Spermatogenesis			
Increased the GSH concentrations.	It is associated with sperm maturation.	Human	Covarrubias *et al.* (2008)
	It is required for sperm nuclear decondensation and formation of the male pronucleus.	Mammals	Dumollard *et al.* (2009)
Spermatid-specific thioredoxins (Sptrx1) has a distinctive distribution in the fibrous sheath.	It is important to the sperm tail elongation at late spermatogenesis.	Human	Yu *et al.* (2002)
Spermatid-specific thioredoxins (Sptrx3) is localized in the Golgi apparatus.	It is necessary for the spermatogenesis process.		Jimenez *et al.* (2004)
Marked expression of vitamin E.	It regulates the signal transduction events and participates in spermatogenesis.	Rat	Bensoussan *et al.* (1998), Palmer & Paulson (1999) and Gopalakrishna & Jaken (2000)
	It is one of the major membrane protectants against ROS and LPO in testis.	Human	Surai *et al.* (1998) and Akiyama (1999)
	It is important in maintaining the physiological integrity of testis, epididymis and accessory glands, which is critical in spermatoge spermatogenesis and sperm maturation thus improving sperm quality and quantity. It may have effect on sexual function by regulating the secretion of gonadotropin in anterior pituitary, then playing a positive role in promotion of spermatogenesis and semen motility.	Chicken	Cerolini *et al.* (2006)
Lack or deficiency of Vitamin E.	It causes abnormal spermatogenesis.	Both human and animals	Brigelius-Flohe & Traber (1999)
	It may lead to reproductive organ damage, such as degenerative spermatogonium, testicular damage and degeneration of the seminiferous tubules.	Rat	Wu *et al.* (1973) and Wilson *et al.* (2003)
Obvious expression of ascorbic acid.	It is important to the testicular differentiation (antioxidant in semen), integrity and steroidogenic functions and thus protects sperm from oxidative damage.	Rabbit	Luck *et al.* (1995), Salem *et al.* (2001), Castllini *et al.* (2003), Yousef *et al.* (2003) and Yousef (2005)
Marked expression of vitamins C and E.	It ameliorates oxidative stress-related testicular impairments in animal tissues.	Rat	Ghosh *et al.* (2002), Kujo (2004), Thews *et al.* (2005) and Marchlewicz *et al.* (2007)
Deficiency in ascorbic acid and vitamin E.	It results in disturbances in spermatogenesis.	Guinea pigs	Chinoy *et al.* (1986)
		rat	Bensoussan *et al.* (1998)
Vitamin A deficiency.	It results in male infertility due to the degeneration of most germ cells.	Both human and rat	Kim & Wang (1993)
Marked expression of selenoprotein phospholipid hydroperoxide glutathione peroxidase (PHGPx).	It plays a crucial role in mammalian male fertility (reduce the intracellular membrane phospholipid hydroperoxides).	Rat	Godeas *et al.* (1997)
Obvious expression of testicular γ-glutamyl transpeptidase (GGT), a membrane bound enzyme involved in amino acid transport across the plasma membrane.	It is essential to the metabolism of the antioxidant glutathione and, as such, is believed to be fundamental to the protection of cells against oxidative stress through the regulation of glutathione levels in Sertoli cell.		Hanigan & Ricketts (1993), Markey *et al.* (1998) and Ojha *et al.* (2006)
Marked expression of melatonin.	It simulates testis growth.	Mink	Maurel *et al.* (2002)
Obvious expression of taurine, GSH, GPx, CAT, and SOD.	It prevents oxidative damage in spermatozoa.	Bovine	Bucak *et al.* (2010)
Marked expression of hypotaurine and taurine.	It is important to gamete maturation and sperm capacitation, and has protective effects against	Cows and goats	Guérin & Ménézo (1995)

	peroxidative damage.		
II- Oogenesis			
Adequate or increase GSH concentrations.	It is necessary for the viability of oocytes and oocyte maturation.	Mammals	Knappen *et al.* (1999) and Fujii *et al.* (2005)
	It has been reported as a co-factor in thiol-disulfide exchange reactions in eggs and in the protection of protein-thiol groups (-SH).	Sea urchin	Sakia (1967) and Ahmed (2005)
Inhibition of GSH synthesis during oocyte maturation.	It gives rise to one-cell zygotes with one pronucleus and one set of condensed DNA.	Mammals	Perreault *et al.* (1988) and Sutovsky & Schatten (1997)
High SOD activity in growing and ovulated follicles.	It is important to the regulation of follicular development, ovulation and luteal functions.	Rat	Laloraya *et al.* (1989a,b)
Changes in the level of SOD in the uterus during the oestrous cycle.	It is responsible for the regulation of uterine oedema and cell proliferation.		Laloraya *et al.* (1991)
Inhibition of ovulation by SOD in human chorionic gonadotropin (hCG)-treated animals.	It may play role in the concentration of $\dot{O}_2^-$ in the mechanism of gonadotropin-induced ovulation.		Sato *et al.* (1992)
High SOD1 expression and activity in corpus luteum during early pregnancy.	It is necessary for the regulation of luteal function.	Human	Sugino *et al.* (2000)
SOD1-deficient.	It causes that oogenesis halted at the middle of follicle development.	Female mice	Matzuk *et al.* (1998)
Change in activities of SOD1, SOD2, GPX, GR and GST during oestrous cycle.	These effects may be linked to ROS generated in the luteal cells, and may be involved in the inhibition of apoptosis and maintenance of luteal steroidogenesis.	Ovine corpus luteum	Al-Gubory *et al.* (2005)
Enhanced SOD1, GPx and GST activities in corpus luteum during early pregnancy.	It is responsible for the rescue of corpus luteum from apoptosis.	Sheep	Al-Gubory *et al.* (2004)
Enhanced CAT and GPX activities and GSH levels in oviduct during the oestrous cycle.	It is important to the control of H_2O_2 during fertilization.	Cow	Lapointe & Bilodeau (2003)
Marked expression of CAT, Cu/ZnSOD, MnSOD, GPx, and γ-glutamylcysteine synthetase (GCS).	It protects the oocyte against peroxidative damage.	Rabbit	Li *et al.* (1993)
		Human and mice	El Mouatassim *et al.* (1999)
Obvious expression of GPx.	It provides insights on the regulation of ROS in the ovarian maturation process.	Shrimp	Ahmed (2005)
Marked expression of taurine in oviduct fluids.	It is an important protector of cells against accumulation of ROS when they are exposed to aerobic conditions.	Human	Miller & Shultz (1987) and Holmes *et al.* (1992)
III- Fertilizations, blastogenesis and organogenesis			
SOD1-deficient.	It causes a drastically compromised fertility.	Female mice	Matzuk *et al.* (1998).
Different superoxide scavengers.	It prevents the blastocyst from hatching, supporting the essential role of ROS in this process.	Mouse	Covarrubias *et al.* (2008)
A decline in antioxidant defence (GSH) and elevated oxidation of proteins, lipids, and DNA of mitochondria.	It may cause a decline of mitochondrial function that affects fertilization and development.	Mammals	Tarin (1996)
		Human	Wilding *et al.* (2001)
		Mice	Thouas *et al.* (2005)
Reduction of GSH and NADPH levels to 45%.	It results in an oxidation of the intracellular redox state.		Dumollard *et al.* (2007)
Recovery of GSH after depletion in two-cell and blastocyst-stage embryos.	It plays a protective role for GR in the GSH redox cycle.		Gardiner & Reed (1994)
Reduction in the GSH pool.	It may result in DNA damage, cell cycle, development arrest and increased susceptibility to oxidative damage.		Goto *et al.* (1992)
		Human	Messina & Lawrence (1989)
Marked expression of GSH.	It participates in various critical cellular processes including detoxification and the regulation of cellular proliferation and development.	Toad early embryos	Kosower *et al.* (1969)
		Black Sea animals	Alien & Balin (1989) and Rudneva (1999)
High uterine PO activity at the time of blastocyst attachment.	It is important to the protection process against deleterious H_2O_2 action.	Rat	Baiza-Gutman *et al.* (2000)

High glutathione S-transferase Mu2 (GSTm2) expression in the uterine epithelium.	It is responsible for the uterine preparation for blastocyst implantation.	Mouse	Ni *et al.* (2009)
Marked expression of ascorbic acid.	It plays critical roles in growth and fertility.	Petromyzon marinus	Moreau & Dabrowski (1998)
Obvious expression of vitamin A (retinol).	It is a fundamental for reproductive and proliferative processes.	Human	Baker *et al.* (2002) and Herrera *et al.* (2004)
	It may have some antioxidant effect by improving blastocyst development morphogenesis and differentiation.	Sheep	Maden (2000) and Livingston *et al.* (2009)
Marked expression of retinoid.	It plays important roles in many diverse biological functions such as cell growth and reproduction.		Livingston *et al.* (2009)
Protein-thiol group oxidation.	It delays cell division and embryonic development.	Mice	Goto *et al.* (1992)
Obvious expression of hypotaurine and taurine.	It is important to fertilization process and has protective effects against peroxidative damage.	Human	Guérin & Ménézo (1995)
Marked expression of hypotaurine.	It is important to the development of *in vitro*-fertilized embryos.	*In vitro* culture (hamster embryo)	Barnett & Bavister (1992)
Obvious expression of mineral element.	It is essential for organogenesis and tissue formation and therefore, their function in pregnancy is fundamental.	Dog	Vannucchi *et al.* (2007)
IV- Embryos and newborns			
Adequate or increase GSH concentrations.	It is associated with embryo maturation.	Human	Fujii *et al.* (2005) and Covarrubias *et al.* (2008)
Increased SOD activity during uterine deciduoma development.	It is responsible for the differentiation and control of decidual cell.	Rat	Devasagayam *et al.* (1990)
Decreased SOD activity and increased lipid peroxide in the endometrium of the late secretory phase.	It is important to endometrium shedding.	Human	Sugino *et al.* (1996)
SOD1 knock-out females exhibit marked increase in post-implantation embryo death.	Oxygen free radicals may cause abnormality of female reproduction in mammals.	Mouse	Ho *et al.* (1998)
Overexpression of CAT and/or SOD2.	It inhibits proliferation of vascular smooth muscle cell.	Human	Brown *et al.* (1999)
		Mice	Shi *et al.* (2004)
Obvious expression CAT, Cu/ZnSOD, MnSOD, GPx, and γ-GCS.	It protects the embryo against peroxidative damage.	Rabbit	Li *et al.* (1993)
		Human and mouse	El Mouatassim *et al.* (1999)
Enhanced CAT, SOD and GPx activities in placental and fetal tissues.	It is responsible for the protection process against ROS toxicity in the feto-placenal system.	Human	Qanungo & Mukherjea (2000)
Enhanced CAT and GPx, acivities, and GSH levels in placental tissue.	It enhances the control of H_2O_2 and stimulates of placental differentiation.		Jauniaux *et al.* (2000)
Enhanced GPx and GR activities.	It controls in the concentration of H_2O_2 and cell death during placental development.	Sheep	Garrel *et al.* (2010)
Early expression of GST isoenzymes in embryonic tissues.	It is important to the detoxification process of toxic compounds.	Human	van Lieshout *et al.* (1998)
A sudden increase of SOD, CAT, GPx, and GST.	It is necessary for the transformation process of embryonic to larval stage.	Larvae of *M. malcolmsonii*.	Arun & Subramanian (1998)
Antioxidants in feto-placental system and UC blood of neonates prevents oxygen damage.	It prevents LPO by trapping the oxygen free radicals and breaking the peroxidation chain reaction.	Human	Qanungo *et al.* (1999)
Deficiency in antioxidant metalloenzyme co-factors; Fe, Cu and Zn.	It leads to severe structural and functional abnormalities.	Chick embryo	Butler (1983)
Marked expression of vitamin A.	It is fundamental for embryo and fetal development.	Human	Baker *et al.* (2002) and Herrera *et al.* (2004)
Obvious expression of vitamin E.	It plays a crucial role in limiting membrane lipid autooxidation by scavenging free radicals or as a structural component of the cell membrane.		Burton *et al.* (1983) and Chow (1991)

Vitamin E deficiency in the cord blood of full term and premature newborns.	It has long been considered the main cause of susceptibility of the newborn erythrocyte to oxygen damage.		Haga & Lunde (1978)
Deficient selenium dependent GSH in newborns.	This susceptibility to oxidative stress presumably has deleterious consequences in cases of inborn error of metabolism.		Tubman *et al.* (1990) and Bracci & Buonocore (1998)
Deficiency in the trace metals selenium, copper and zinc, essential components of the antioxidant enzymes GPx and superoxide dismutase.	It may act in concert with plasma factors to produce the antioxidant handicap of the newborn.		Bracci *et al.* (1988)
Vitamin E-deficient mothers.	Tissues of pups born will be more sensitive to peroxidative damage.	Rat	Schinella *et al.* (1999)
Marked expression of hypotaurine and taurine.	It is important to the early embryonic development and has protective effects against peroxidative damage.	human	Guérin & Ménézo (1995)
Enriching the culture medium with taurine and melatonin.	It improves *in vitro* embryo production efficiency	Buffaloes	Manjunatha *et al.* (2009)
Obvious expression of taurine.	It may protect embryos from high K^+ concentrations in reproductive tract fluids.	mouse	Dumoulin *et al.* (1992)

7. General Diagram About The Interactions Between Antioxidants And ROS In Pregnant Dams And Their Offspring (Figure 1).

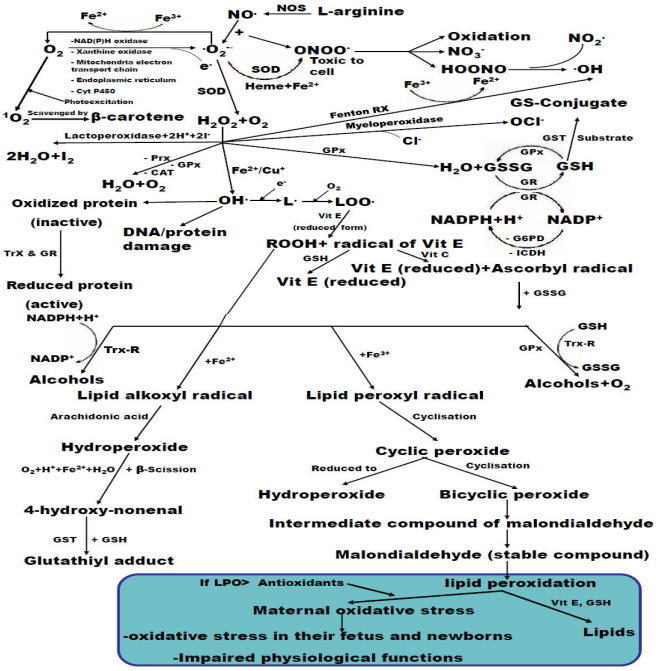

Figure 1. General diagram about the interactions between antioxidants and ROS in pregnant dams and their offspring.

8. Chemical Toxicity Associated With Oxidative Stress During Development

Environmental pollutants, such as compounds used in agriculture or deriving from vehicles, industries and human activities, can represent a major concern for human health since they are considered to be involved in many disease states with major public health significance (Braconi *et al.* 2011; Ahmed 2013). Also, Poljšak *et al.* (2011) reported that free radicals and ROS are involved in toxic mechanisms of action of certain air pollutants, metals, ionizing and nonionizing radiations, alcohols, and pesticides being implicated. A broad variety of pollutants in the aquatic environment have the capacity to give rise to toxic effects expressed as cellular OS (Farmen *et al.* 2010). In animals, the egg and larval stages are the most susceptible to environmental stress (Rudneva 1999; Menon & Rozman 2007). In addition, there were oxidative stress and DNA damage in a mercury exposure workers (Al-azzawie *et al.* 2013). Roopha & Latha (2013) reported that cadmium exposure-induced oxidative stress; delay in sexual maturation and impaired hormones in developing rat ovary. Epidemiological and experimental data indicate that the in utero exposure to environmental chemicals during pregnancy can mediate early embryonic losses, spontaneous abortion, fetal growth retardation and resorptions, decreased litter size, fetal malformations and low birth weight (Bajaj *et al.* 1993; Friedler 1996; Khattak *et al.* 1999; Buczynfiska & Tarkowski 2005), at least in part, via ROS production which damages cellular macromolecules and/or changes signal transduction (Wells *et al.* 2005). The teratogenicity of such chemicals depends upon their bio-activation by cytochrome P450 enzymes, prostaglandin H synthases and lipoxygenases, resulting in ROS-induced OS, and this in turn affects cellular macromolecules, leading to in utero embryonic and fetal death (Wells *et al.* 2005). Several consequences for human and animal reproductive systems are known as these chemicals disrupt endocrine function and contribute to alterations in growth and development (Sanderson 2006). In utero exposure to xenobiotics induces OS and fetal toxicity that may eventually cause cancer later in life (Wan & Winn 2006). Also, Fowler *et al.* (2008) reported that exposure of ovine fetus to prolonged low dose of environmental chemicals adversely affects fetal ovarian development, at least in part, through antioxidative pathways alteration and apoptosis induction. Xenobiotic substances are becoming an increasingly main environmental problem in sewage treatment systems and xenobiotics-enhanced OS may cause birth defects (Wells *et al.* 2009). In addition, Thompson and Bannigan (2008) speculated that environmental heavy metals have the potential to affect reproduction and development at every stage of the reproductive process. Methylmercury (MeHg) is a ubiquitous environmental pollutant to which humans can be exposed by eating contaminated food, particularly through the consumption of fish and fish products (Bourdineaud *et al.* 2008). Grandjean *et al.* (1997) undertook that MeHg has serious adverse effects on the development of the human central nervous system (CNS), particularly when exposure occurs prenatally. Moreover, MeHg is toxic through multiple mechanisms, including ROS formation (Sarafian & Verity 1991; Ali *et al.* 1992; Yee & Choi 1994), likely due to a less efficient ROS detoxifying system and lower activity of mitochondrial enzymes in tissue from young animals (Dreiem *et al.* 2005). Generally, Huang *et al.* (2010) reported that the hatching, survival, growth and antioxidant biomarkers of the flounder embryos and larvae were susceptible to the highest mercury concentrations and could thereby serve as potential biomarkers for evaluating mercury contamination in the aquatic environment. Also, Richetti *et al.* (2011) recorded that mercury chloride may cause a disturbance in the electric signal transmission, through alterations in cholinergic transmission, and also in the antioxidant competence of zebrafish brain tissue. In rat, the fluoride impaired OS and biometal deformations are synergistic that consecutively governs the neuronal damage and developing CNS no longer prevents exacerbations of fluoride (Narayanaswamy & Piler 2010). Prenatal exposure to other heavy metals, especially lead and cadmium, induces OS through impairment of the antioxidant defense systems in the brain, liver and kidney of the developing fetuses (Uzbekov *et al.* 2007; Chater *et al.* 2008a,b). Cadmium-enhanced ROS generation which considerably increased the oxidative products of proteins measured as carbonyls was effectively inhibited by zinc supplementation (Aravind *et al.* 2009; Zhang *et al.* 2011). In pregnant rats and fetuses, cadmium may induce OS in liver, kidney and placental tissues (Enli *et al.* 2010). Cadmium may generate the ROS and carbon-centered radical species by participation of both iron mediation through iron-catalyzed reactions and activation of Kupffer cells, the resident liver macrophages (Liu *et al.* 2008a). Cadmium induces autophagy in skin epidermal cells (Son *et al.* 2011). Also, cadmium initiates the caspase-independent death in mouse mesangial cells (Liu & Templeton 2008). Studies have demonstrated that ROS can induce or mediate the activation of the mitogen-activated protein kinase (MAPK) pathways (McCubrey *et al.* 2006). This mechanism is unclear. Because ROS can alter protein structure and function by modifying critical amino acid residues of proteins (Thannickal & Fanburg 2000), the oxidative modification of signaling proteins by ROS may be one of the plausible mechanisms for the activation of MAPK pathways. However, the precise molecular target(s) of ROS is unknown. The prevention of oxidative stress by antioxidants blocks MAPK activation after cell stimulation with cellular stimuli indicating the involvement of ROS in activation of MAPK pathways. The other observations provide a strong argument for activation of MAPK pathways by direct exposure of cells to exogenous H_2O_2 (Ruffels *et al.* 2004; Son *et al.* 2011). On the other hand, the mechanism of ROS-induced modifications in ion

transport pathways involves the inhibition of membrane-bound regulatory enzymes and modification of the oxidative phosphorylation and ATP levels (Su *et al.* 2007).
In addition, in goldfish, both chromium ions (III and VI) induced OS and affected the activity of antioxidant and associated enzymes (Kubrak *et al.* 2010). Moreover, sublethal waterborne zinc is an oxidative stressor in fish, and emphasizes the vital protective role of higher salinities in ameliorating the OS associated with zinc toxicity in estuarine teleost (Loro *et al.* 2012). Taken together, Kubrak *et al.* (2011) reported that exposure of goldfish to cobalt ions may result in the development of OS and the activation of defense systems. Impaired oxidant/antioxidant status is related to a variety of pregnancy complications, and the lead-induced OS may be one of the underlying mechanism(s) of preterm delivery and highlights the importance of evaluating the impact of persistent environmental pollutants on adverse pregnancy outcome (Ahamed *et al.* 2009). Rodríguez-Estival *et al.* (2011) speculated that certain physiologic disorders, attributed to lead exposure are related to the generation of OS. Collectively, the higher lead and cadmium concentrations in blood cause an increase of SOD activity (Wieloch *et al.* 2012). In rats, fluoride and ethanol exposure induces substantial changes in LPO, antioxidant defense, and morphology of intestine, which may affect its functions (Chauhan *et al.* 2011). Moreover, Hannas *et al.* (2010) demonstrated that nitrite elicits developmental and reproductive toxicity at environmentally relevant concentrations due likely to its intracellular conversion to nitric oxide. A mechanistic study in mice has shown that ROS may play a main role in benzene-mediated fetal hematotoxicity (Wan & Winn 2008; Badham & Winn 2010). Generally, several studies have focused on metal-induced generation of ROS in metal toxicity and carcinogenicity, underscoring the significance of OS in metal action in biological systems (Leonard *et al.* 2004; Valko *et al.* 2005 & 2006; Liu *et al.* 2008b). Metal overload reduces antioxidants in the cell by binding to reduced GSH, metallothioneins and Trxs (Ma 2009). Metal toxicity is related to their oxidative state and reactivity with other compounds (Koivula & Eeva 2010). In general terms, increased levels of antioxidant enzymes, in gill tissues of mussels, at some sites suffering from metal and organic pollution indicated a situation of OS that nevertheless did not appear to be harmful, since LPO levels showed no peroxidative damage (Fernández *et al.* 2010). Interestingly, in growing chicks, environmental intoxication causes an increase of lipoperoxidation and impairs the response of their immunological system (Kamiński *et al.* 2009).
During pregnancy, the contamination by xenooestrogen bisphenol-A (BPA) is confirmed by its presence in urine, blood, amniotic fluid and placental and fetal tissues (Vandenberg *et al.* 2007; Lee *et al.* 2008b). During the embryonic/fetal development, exposure of rodents to BPA induces tissue OS, ultimately resulting in maldevelopment of several organs as brain, kidney and testis (Kabuto *et al.* 2004), disturbances of postnatal reproductive functions (Rubin *et al.* 2001; Hong *et al.* 2005; Markey *et al.* 2005) and behaviorally sex difference (Palanza *et al.* 2008). Also, Gotti *et al.* (2010) reported that the alteration of the neuronal nitric oxide synthase expression may be one of the causes of the important behavioral changes noticed in bisphenol-exposed mice. Several actions have been proposed for the toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and its congeners (Safe 1990; DeVito & Birnbaum 1994; Pohjanvirta & Tuomisto 1994; Van den Berg *et al.* 1994), where OS is being considered as one of the important ones (Stohs *et al.* 1990 & 1991). The administration of single acute doses of TCDD to laboratory animals induces the generation of ROS (Bagchi & Stohs 1993; Alsharif *et al.* 1994), LPO (Stohs *et al.* 1983 & 1990) and DNA damage (Wahba *et al.* 1988; Stohs *et al.* 1990), and decreases membrane fluidity (Alsharif *et al.* 1990) and GSH (Stohs *et al.* 1990) in liver and other tissues. These observations have been reported by the study of Slezak *et al.* (1999) who have demonstrated considerable increases in hepatic $O_2^{\bullet-}$ production and LPO as well as significant inhibition of the levels of GSH and α-tocopherol after seven days acute exposure of mice to TCDD. Also, long-term exposure of mice to TCDD leads to the induction of biomarkers of OS, including generation of ROS, LPO and DNA damage in liver and brain tissues (Hassoun *et al.* 1998; Alsharif *et al.* 1999; Tang *et al.* 1999; Slezak *et al.* 1999). Hassoun *et al.* (2000 & 2002) demonstrated that subchronic and chronic exposure of rats to TCDD leads to dose- and time-dependent increases in the production of ROS, LPO, and DNA damage in the whole brain tissue homogenate. TCDD, a potent developmental teratogen (Ahmed 2011) inducing OS and sublethal changes in multiple organs, provokes developmental chicken renal injuries (Lim *et al.* 2008). In rats, Hassoun *et al.* (2000) found that subchronic exposures to TCDD, 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) and 3,3',4,4',5-pentachlorobiphenyl (PCB126) cause a significant oxidative damage in liver and brain tissues, with more damage reported in the brain as compared to the liver tissues. Polychlorinated biphenyls (PCBs) have been shown to produce transient ROS in rat synaptosomes (Voie & Fonnum 2000), liver (Twaroski *et al.* 2001; Tharappel *et al.* 2008), cerebellar granule cells (Mariussen *et al.* 2002) and neutrophils (Narayanan *et al.* 1998). Even though the transduction pathways involved in the elevated ROS production in neurons are not well defined, several studies show that PCB exposure stimulates quick elevations in intracellular Ca^{2+}, suggesting that Ca^{2+}-mediated signaling pathways are potentially involved in neuronal adaptive and toxic responses (Shafer *et al.* 1996; Bemis & Seegal 2000; Inglefield *et al.* 2001; Lee & Opanashuk 2004). Prenatal-stress-induced neuronal damage in offspring is multifactorial, including oxidative damage in the developing brain (Madhyastha *et al.* 2013). In addition,

increasing evidence in animal models links TCDD and benzo[a]pyrene (BAP) with OS, and these compounds are easy to increase cancer risk in certain organs (Kim & Lee 1997; Yoshida & Ogawa 2000; Emre *et al.* 2007). BAP exposure leads to DNA and protein oxidation and alterations in SOD and CAT activities in liver and kidney (Kim & Lee 1997). Furthermore, Emre *et al.* (2007) reported that BAP administration alone, or together with ethanol, induces changes in GSH and MDA levels, and in SOD activity in the lung and brain with varying degrees of histological changes. In animal models, the unfavorable developmental events of in utero exposure to agents like thalidomide, methamphetamine, phenytoin, BAP, and ionizing radiation can be modulated by changing pathways that control the embryonic ROS balance, including enzymes that activate endogenous substrates and xenobiotics to free radical intermediates, antioxidative enzymes that detoxify ROS, and enzymes that repair oxidative DNA damage (Wells *et al.* 2009). Furthermore, Chen *et al.* (2006) observed that increased OS in blood samples from workers exposed to polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans. Developmental polybrominated diphenyl ethers (BDE-99) exposure induces OS in the hippocampus of offspring by changing the activity of different antioxidant enzymes and producing free radicals (Cheng *et al.* 2009). Several investigators (KonKim *et al.* 2004; Marczynski *et al.* 2002; Singh *et al.* 2007) also revealed that increased oxidative DNA damage as well as up regulation of genes and proteins involved in OS occurs in individuals exposed to environmental air pollutants such as halogenated aromatic hydrocarbons, dioxins, and particulate matter. Moreover, Cavallo *et al.* (2006) speculated that occupational exposure to halogenated aromatic hydrocarbons has also been linked to oxidative DNA damage.

Pesticides are another example of agents that act as pro-oxidants and elicit actions in various tissues. In some cases, these prooxidant effects occur alongside pesticide-induced changes in target enzymes, many of which share in neurotransmitter metabolism (Limón-Pacheco & Gonsebatt 2009). Pesticide exposure of fish caused increase in MDA and fluctuated antioxidant system along with inhibited acetyl cholinesterase (AChE) (Sharbidre *et al.* 2011). For example, paraquat has been broadly studied as an OS inducer, and paraquat toxicity is thought to mainly result from ROS generation and alterations in redox cycling (Dinis-Oliveira *et al.* 2008). In rats, paraquat induces alterations in antioxidant systems in many tissues (e.g., liver, blood, kidney, lung), and its targets include GSH, GR, CAT, SOD, GPx, and GST (Aoki *et al.* 2002; Tomita *et al.* 2005; Ray *et al.* 2007). Malathion, an organophosphorus compound, is another example of a pesticide that induces OS in rats, resulting in generation of free radicals and changes in antioxidant systems in several organs (Akhgari *et al.* 2003). Also, exposure of laboratory animal to high concentrations of a single heavy metal might lead to its accumulation and potentially, oxidative damage (Halliwell & Gutteridge 1999). Parquet results in two potentially critical consequences relevant to the toxicity (Limón-Pacheco & Gonsebatt 2009): **(i)** production of ROS including $O_2^{\bullet-}$, H_2O_2 and $^{\bullet}OH$, and **(ii)** oxidation and reduction of reducing equivalents (NADPH, GSH, etc); both share in the initiation of OS and damage to the tissue. Arsenic induces a broad diversity of toxic and carcinogenic effects in humans, including cancers in skin, lung, bladder, kidney, and liver. There are reports also of skin lesions, nerve damage and cardiovascular lesions such as atherosclerosis (ATSDR 2007). Furthermore, Arsenic-mediated generation of ROS is a complex process that involves a variety of ROS including $O_2^{\bullet-}$, O_2, $RO_2^{\bullet}$, $NO^{\bullet}$, H_2O_2, dimethylarsinic peroxyl radicals, and the dimethylarsinic radical (Ma 2009). Severe oxidative damage to macromolecules causes cellular death. In addition, methyl parathion (MP), an organophosphate extensively applied in agriculture and aquaculture, mediates OS and alters the antioxidant defense system (Monteiro *et al.* 2009). Also, Stara *et al.* (2012) reported that the prolonged exposure of common carp (*Cyprinus carpio* L.) to simazine, an s-triazine herbicide normally present in aquatic environments, leads to excess of ROS formation resulting in oxidative damage to cell lipids and proteins and also inhibited antioxidant capacities. Several environmental pollutants engage signaling pathways that are activated in response to OS. Also, redox signaling caused by environmental stressors involves both changes in antioxidant defenses (such as decreases in GSH/GSSG ratio) and accumulation of ROS leading to OS (Mena *et al.* 2009). In general, antioxidant enzymes play vital roles in the protection against oxidative damage caused by environmental pollutants by scavenging high levels of ROS and have been quantified as OS markers (Nair *et al.* 2011). OS seems to be the essential aspect in the regulation of the apoptotic pathways triggered by environmental stressors (Franco *et al.* 2009). These biochemical alterations mediate a number of redox dependent processes such as oxidative protein modifications, oxidative DNA damage and changes in mitochondrial function which in turn trigger the activation of specific signaling cascades. These effects are dose- and age-dependent. Also, varying levels of metals and contaminants due to different age, gender, genetic susceptibility, diet were probably the main explanations for the species differences in antioxidant defense. Thus, understanding the pathways resulting in the initiation of antioxidant responses will allow development of strategies to protect against oxidative damage.

9.Diagram Of The Effect Of Environmental Pollutants On The Maternal ROS And Antioxidants During The Development Of Their Offspring (Figure 2)

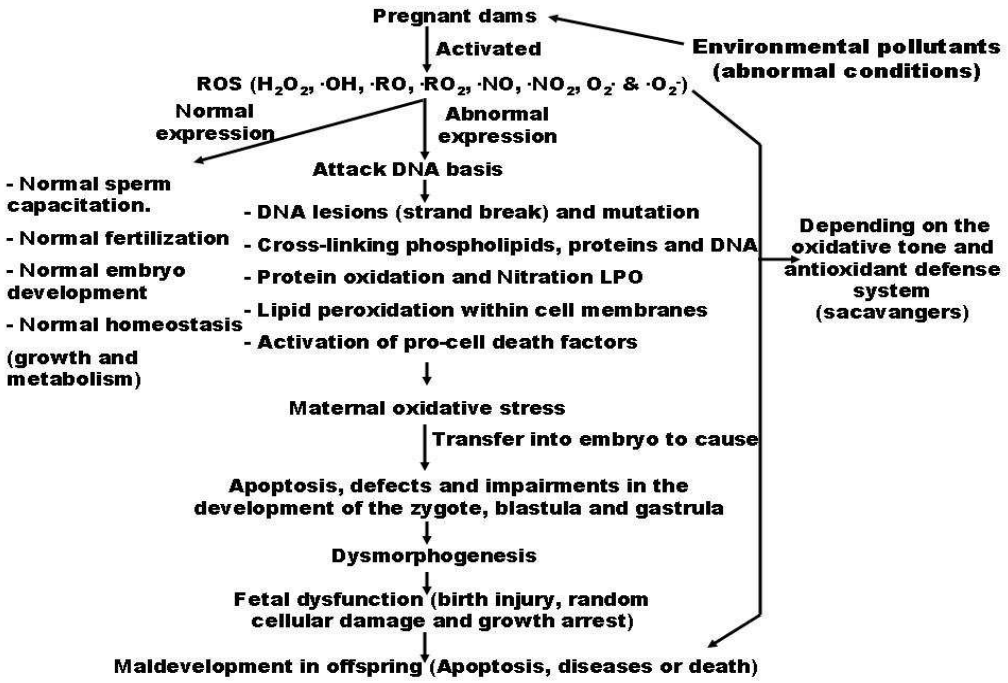

Figure 2. Diagram about the effect of environmental pollutants on both dams and their offspring

10. General Diagram About The Effect Of Environmental Pollutants On The Antioxidant-Reactive Oxygen Species System (Table 6 and Figure 3)

Table 6. Effect of environmental pollutants on the pro-oxidant/anti-oxidant balance in different species.

Environmental pollutants	Effect	Species	Reference
I- Aromatic hydrocarbons			
- TCDD	- It induces ROS and causes apoptosis via the activation of the aryl hydrocarbon receptor (AhR).	Zebra fish	Dong *et al.* (2001)
	- It induces the production of ROS, LPO and DNA damage.	Rat	Stohs *et al.* (1990) and Bagchi & Stohs (1993)
	- It causes a substantial increase in TBARS (thiobarbituric acid reacting substances) production in whole brain.		Hassoun *et al.* (2000 & 2003)
	- It causes a depletion of GSH, and inhibition of GPx activity.		Stohs *et al.* (1984), Hassan *et al.* (1985) and Vuchetich *et al.* (1996)
	- It induces oxidative stress.		Venkataraman *et al.* (2004)
		Bird	Hilscherova *et al.* (2003)
		Fish	Vega-Lopez *et al.* (2006)
		Hatchling chicken (*Gallus domesticus*)	Hilscherova *et al.* (2003)
	- It causes oxidative stress which following the production of reactive	Mice	Schetzer *et al.* (1998)
		Fish	Cantrell *et al.* (1996)

	oxygen species can cause embryolethality and teratogenicity.	Rat	Hassan *et al.* (1985)
	- It causes a significant increase in LPO in liver and adipose tissue on both day 1 and day 40 post-treatment.	Guinea pigs	Ashida *et al.* (1996)
- Dibenzo-p-dioxins (PCDDs)	- It produces ROS that overcome the protection afforded by antioxidant defense mechanisms, thereby leading to oxidative damage which is manifest by damage to tissue macromolecules including DNA, proteins and lipids.	Aquatic animals	Di Giulio *et al.* (1989)
- PCBs	- It decreases vitamin C content in testis.	Rat	Murugesan *et al.* (2005b)
	- It alters membrane bound ATPases and cholinergic function by inducing oxidative stress in different brain regions.		Venkataraman *et al.* (2008)
	- It is responsible for oxidative stress status and teratologic effects in embryos.	Chick	Jin *et al.* (2001)
	- It decreases the concentrations of antioxidant enzymes' activity and increases the concentration of LPO and H_2O_2 generation.	Rat	Muthuvel *et al.* (2006)
	- It induces ROS and oxidative stress.	Bird	Hoffman *et al.* (1996)
		Fish	Ruiz-Leal & George (2004)
- 2,3,7,8-tetrachlorodibenzofuran		Lake Sturgeon *(Acipenser fulvescens)*	Palacea *et al.* (1996)
- PeCDF	- It induces significant oxidative damage in the hepatic and brain tissues.	Rat	Hassoun *et al.* (2000)
- PCB 126	- It causes oxidative stress which is suggested by a similar decrease in GPx activities and increase in the oxidized to GSH ratio and in the LPO.	Birds (American kestrels)	Hoffman *et al.* (1996)
		Chicken eggs	Jin *et al.* (2001)
- PCB (Aroclor 1254)	- It increases H_2O_2 and LPO levels. - It declines the activity of GPx. - It decreases the level of vitamin C content and GSH. - It induces oxidative stress in brain by decreasing the activities of antioxidant enzymes.	Rat	Venkataraman *et al.* (2007)
	- It induces oxidative stress and decreases the activities of antioxidant enzymes in the ventral prostate and testicular Leydig and Sertoli cells.		Krishnamoorthy *et al.* (2005) and Murugesan *et al.* (2005a)
	- It induces cytotoxicity in brain.		Mariussen *et al.* (2002)
- A1242	- It induces production of ROS in a concentration-dependent manner.		
- BAP	- It leads to DNA oxidation, protein oxidation, and alterations in SOD and CAT activities.		Kim & Lee (1997)
- BPA	- It induces tissue oxidative stress, ultimately leading to underdevelopment of the brain, kidney and testis, and to disturbances of postnatal reproductive functions.		Hong *et al.* (2005)
		Mice	Kabuto *et al.* (2004) and Markey *et al.* (2005)

- Naphthalene (NAP)	- It produces $^{\bullet}OH$ and oxidative damage in liver	Freshwater goldfish (*Carassius auratus*)	Shi et al. (2005)
	- It induces LPO and tissue damage.	Mice	Bagchi *et al.* (2002)
	- It produces ROS which may lead to enhanced LPO, enhanced excretion of urinary lipid metabolites, as well as other cell-damaging effects, including membrane and DNA damage and glutathione depletion.	Rat	Vuchetich *et al.* (1996)
	- It results in elevated levels of serum lipid peroxides with a concomitant decrease in GSH levels in lenses, suggesting enhanced LPO.		Yamauchi *et al.* (1986)
	- It induces oxidative stress *in vivo* based on increased hepatic and brain LPO, GSH depletion, increased DNA-single strand breaks and membrane microviscosity, and elevated excretion of the urinary lipid metabolites MDA, formaldehyde, acetaldehyde and acetone.		Vuchetich *et al.* (1996)
	- It induces oxidative stress by producing ROS.	Marine organisms (crab and macroalga)	Collen *et al.* (2003), Lee & Shin (2003) and Vijayavel *et al.* (2004)
- Endrin	- It induces oxidative stress and tissue damage in the liver and brain tissues.	Mice	Bagchi *et al.* (2002)
	- It induces the production of $O_2^{\bullet -}$ by peritoneal macrophages as well as hepatic mitochondria and microsomes.	Rat	Bagchi *et al.* (1993a,b)
II- Pesticides			
- Organophosphorus	- It induces apoptosis in immune and neural cells via the mitochondrial pathway.	Human neuroblastoma cells	Carlson *et al.* (2000)
		Human lymphocytes	Das *et al.* (2006)
	- It causes oxidative attack in spermatozoa, including single- and double-DNA strand breaks, cross-links, chromosomal aberrations and DNA base oxidation.	Human	Hughes *et al.* (1996), Lopes *et al.* (1998), Twigg *et al.* (1998), Banerjee *et al.* (1999) and Ranjbar *et al.* (2002)
	- It induces oxidative stress.	Rat	Debnath & Mandal (2000) and Sharma *et al.* (2005)
- Chlorpyrifos	- It induces caspase dependent apoptosis associated to oxidative stress.	Human monocyte cell line U937	Nakadai *et al.* (2006)
- Dichlorvos		Human T cells	Li *et al.* (2009)
		Rat brain	Kaur *et al.* (2007)
		Mouse retina	Yu *et al.* (2008)
- Dichlorodiphenyldichloroethane (DDT)	- It induces apoptosis via GSH depletion and oxidative stress triggering the intrinsic mitochondrial apoptotic pathway.	Human T-cell leukemic line	Kannan *et al.* (2000)
		Human blood mononuclear cells	Perez-Maldonado *et al.* (2005) and Ahmed *et al.* (2008)
		Rat brain	Kaur *et al.* (2007)
- Endosulfan		Cultured rat Sertoli cells	Song *et al.* (2008)
- Dieldrin			

- Thiram	- It induces GSH depletion which is paralleled by protein carbonylation, LPO and subsequent apoptotic cell death.	Chinese hamster fibroblasts	Grosicka *et al.* (2005)
- Asmancozeb	- It induces oxidative stress, DNA damage and activation of the mitochondrial pathway of apoptosis.	Rat	Calviello *et al.* (2006)
- Piperonyl butoxide (PBO)	- It induces the increase of ROS and oxidative stress.		Muguruma *et al.* (2007)

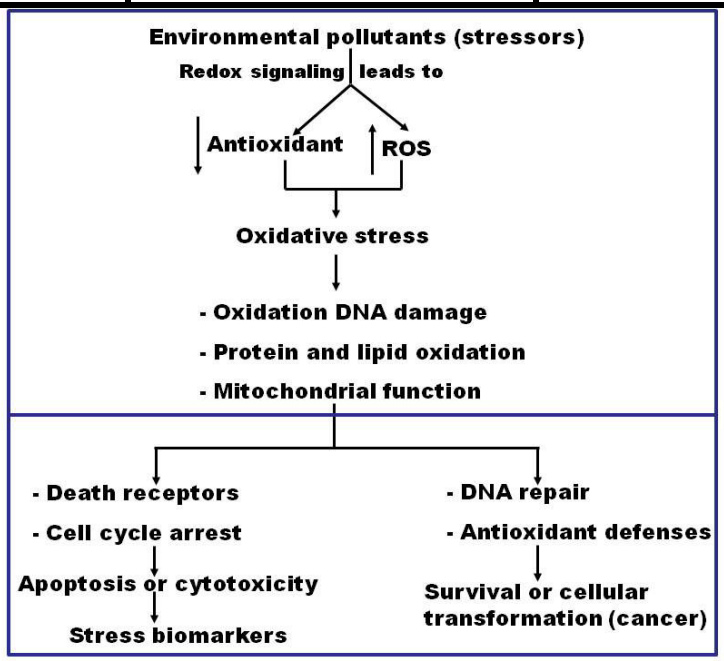

Figure 3. General diagram about the effect of environmental pollutants on the antioxidant-reactive oxygen species system.

11. Abbreviations

$^{\bullet}OH$ = Hydroxyl radical
$^{1}O_2$ = Singlet oxygen
AChE = Acetyl cholinesterase
ADP = Adenosine diphosphate
AhR = Aryl hydrocarbon receptor
ATP = Adenosine triphosphate
BAP = Benzo[a]pyrene
BBM = Brush-border membrane
BDE-99 = Polybrominated diphenyl ethers
BPA = Bisphenol-A
CAT = Catalase
CLO^{-L}= Hypochlorite
CNS = Central nervous system
Cyt P450 = Cytochrome P450
DDT = Dichlorodiphenyldichloroethane
DUOXs = Thyroid oxidases
EC-SOD = Extracellular superoxide dismutase
G6PDH = Glucose-6-phosphate dehydrogenase
GCS = γ-glutamylcysteine synthetase
GD = Gestation day
GGT = γ-glutamyl transpeptidase
GPx = Glutathione peroxidase
GR = Glutathione reductase
GSH = Reduced glutathione

GSSG = Oxidized glutathione
GST = Glutathione-S-transferase
GSTm2 = Glutathione S-transferase Mu2
H_2O_2 = Hydrogen peroxide
hCG = Human chorionic gonadotropin
HO-1 = Heme oxygenase
$HOCl^-$ = Hypochlorous acid
HOONO = Peroxynitrous acid
ICDH = Isocitrate dehydrogenase
IUGR = Intra-uterine growth restriction
$L^\bullet$ = Lipid radical
LDL = Low-density lipoprotein
$LOO^\bullet$ = Lipid peroxy radical
LP = Lactoperoxidase
LPO = Lipid peroxidation
MAPK = Mitogen-activated protein kinase
MDA = Malondialdehyde
MeHg = Methylmercury
MP = Methyl parathion
NADH = Nicotinamide adenine dinucleotide hydrogen
NADP = Nicotinamide adenine dinucleotide phosphate
NADPH = Nicotinamide adenine dinucleotide phosphate hydrogen
NAP = Naphthalene
$NO^\bullet$ = Nitric oxide
$NO_2^\bullet$ = Nitrite radical
NOS = Nitric oxide synthase
NOX = NADPH oxidases
$O_2^{\bullet-}$ = Superoxide
O_3 = Ozone
$ONOO^-$ = Peroxynitrite anion
OS = Oxidative stress
PBO = Piperonyl butoxide
PCa = Protein carbonyl
PCB126 = 3,3',4,4',5-pentachlorobiphenyl
PCBs = Polychlorinated biphenyls
PCDDs = Dibenzo-p-dioxins
PeCDF = 2,3,4,7,8-pentachlorodibenzofuran
PHGPx = Phospholipid hydroperoxide glutathione peroxidase
PND = Postnatal day
PO = Peroxidase
PPO = Polyphenol oxidase
Prx = Peroxiredoxin
$Q^{\bullet-}$ = Semiquinone radicals
RBCs = Red blood cells
RNS = Reactive nitrogen species
$RO^\bullet$ = Alkoxyl radical
$RO_2^\bullet$ = Peroxyl radical
R–O–OH = Hydroperoxide
ROS = Reactive oxygen species
R-SH = Thiol acid
R-S-S-R = Dithio acid
SH = Thiol group
SOD = Superoxide dismutase
Sptrx = Spermatid-specific thioredoxins
TBARS = Thiobarbituric acid reacting substances
TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin
TNF-α = Tumor necrosis factor-α
Trx = Thioredoxins

Trx-R = Thioredoxin reductase
t-SH = Total thiol
UC = Umbilical cord
Vitamin E = α-tocopherol

12. Research Agenda

- Identification of the proteins phosphorylated during sperm capacitation and acrosome reaction as well as proteins that appear to be regulated by a change in sulfhydryl content. These studies should improve the understanding of fertilizing ability by spermatozoa.
- Importance of polymorphisms in the antioxidant pathways for complications of pregnancy.
- The reciprocal regulation of signaling cascades and metabolic pathways during animal development, in which ROS will be a key player.
- The role of epigenetic processes (controlling gene expression) during different developmental periods.
- Understanding of both environmentally induced cytotoxicity/apoptosis and environmentally induced cellular transformation and maternal inflammation during pregnancy is necessary for a complete understanding of the human health consequences to environmental exposures.

13. Disclosure Statement

No actual or potential conflict of interest could inappropriately influence this work.

14. Funding

This work was supported by National Grant from the Research Center, Beni-Suef University, Beni-Suef, Egypt, and from the Italian Ministry for Education, University and Research, General Management for International Research.

15. Acknowledgments

The authors are grateful to Beni-Suef University and Roma Tre University for invaluable help.

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