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Chapter
Importance of Oxidative Stress Mechanism in Reproductive Functions and Infertility
Moyinoluwa Comfort Onaolapo, Samuel Chibueze Nzekwe, Lateef Okeleji Olabisi, Victor Oluwaseyi Amos, Oluwatobi Hezekiah Ajayi and Ayodeji Folorunsho Ajayi

Abstract

Oxidative stress (OS) is a term used to describe the homeostatic oxidation-favoring imbalance between the formation of reactive oxygen species (ROS) or other compounds causing oxidative stress and the countering activities/levels of enzymatic or non-enzymatic antioxidants. The role of OS in reproduction cannot be underestimated in neither health nor disease. This chapter focuses on the roles of OS in spermatogenesis, steroidogenesis and male sexual activity, and also its effects in female folliculogenesis, steroidogenesis, ovulation, luteogenesis, and pregnancy. Furthermore, OS's impact on the efficacy of Artificial Reproductive Techniques (ARTs) was assessed, and the impact of antioxidants on reproductive health and sterility were discussed in both males and females. Through available evidence, it appears that oxidative state impairs reproductive processes and causes general disruptions through inflammation, DNA damage, lipid peroxidation, protein alterations and mitochondrial dysfunction. It will be of importance to identify oxidative stress biomarkers specific for each reproductive process, and it seems that more research should be focused on epigenetic characteristics together with oxidative stress in reproductive health and infertility.

Keywords: female reproduction, health, infertility, male reproduction, oxidative stress

1. Introduction

Oxidative stress connotes the damage that occurs when the activities of reactive oxidants overwhelms the in vivo capabilities of antioxidants [1]. This state is characterized by an elevated amount of reactive species such as superoxide (O$_2^-$), peroxyl (RO$_2^-$), hydroperoxyl (HO$_2^-$), and hydroxyl (-OH), which are products of reaction of oxygen with various unsaturated lipids. Furthermore, since antioxidants constantly respond to the overwhelming oxidative insult, the levels of enzymatic and non-enzymatic antioxidants are often found to be decreased [2]. Among these parameters, those that demonstrate measurable changes are generally called OS biomarkers.
Previous investigations have implicated OS and its mechanisms in a number of diseases, including infertility [3].

Infertility is the inability to achieve conception following 12 months of continual unprotected copulation [4]. Infertility could be a result of dysfunctions from either of the partners or both, it was reported that about 48 million married individuals and a total of 186 million persons are affected by infertility [5, 6]. Similarly, a meta-analysis of researches on the prevalence of infertility suggests that about 10% of the world population lives with infertility [7].

While it must be mentioned that physiological levels of ROS are important for male reproductive processes, it is also essential to state that unchallenged activity of ROS will be, at least in turn, damaging to the health of the spermatozoa and gamete cells [8]. In men, free radical elevation in the ejaculate is mainly sponsored by high leukocyte counts as well as immature spermatozoa, which cause low fertility owing to lipid peroxidation, apoptosis and damage to the DNA of sperm cells [8, 9]. In addition, OS in male infertility is connected with a number of environmental and epigenetic factors like obesity, smoking, poor diet, infection, and exposure to some endocrine disruptors [8]. Furthermore, conditions like varicocele, testicular cancer, idiopathic male infertility and erectile dysfunction have been strongly associated with oxidative stress [10].

In females, disproportionate levels of anti- and pro-oxidants have been associated with conditions like polycystic ovary syndrome (PCOS), endometriosis and unexplained infertility [11]. One of the major ways in which oxidative stress impairs female fertility is its harmful effects on proteins and nucleic acids [11]. Other mechanisms involved in oxidative stress-induced reproductive dysfunction in females include peroxidation of arachidonic acids, release of inflammatory mediators, and apoptosis [12].

Reports have shown OS to be a common denominator in the majority of infertility states in males and females [13]. Therefore, clarifying the role of OS in crucial reproductive processes (spermatogenesis, ovulation, and steroidogenesis) and identifying the vital modulatory roles of antioxidants in these conditions will help to elucidate the subject of infertility which is plaguing the world and can lead to valuable recommendations.

2. Reactive oxygen species

2.1 Definition of reactive oxygen species

Reactive oxygen species (ROS) is a combined terminology ascribed to oxygen radicals, such as hydroxyl (-OH), superoxide (O$_2^-$), hydroperoxyl (HO$_2$) peroxyl (RO$_2$), radicals, and also, a number of non-radical oxidizing agents, such as hypochlorous acid (HOCl), hydrogen peroxide (H$_2$O$_2$), and ozone (O$_3$), which possess at least a single unpaired electron and can be transposed into radicals with ease [14]. They are toxic by-products of aerobic metabolism [15] and they are produced continually at basal levels during metabolic activities in the body. The body’s antioxidant system scavenges ROS and has the capability to neutralize potential harm under physiological conditions [16]. In addition, the redox homeostasis within the cell is maintained by the reducing nature of the internal environment of the cell, thereby preventing injury as a result of free radicals. The environment however, is sustained by a number of antioxidant substances and enzymes, which include glutathione.
peroxidase, superoxide dismutase (SOD), glutathione, other thiols, thioredoxin, ascorbate (vitamin C) and tocopherol (vitamin E) [17]. Although studies have shown that ROS are involved in the pathogenesis of many diseases, they are also reported to be pertinent in a number of functions including signal transduction, gene expression and mitochondrial electron transport [18].

2.2 Types and sources of reactive oxygen species

The types of ROS are not to be limited to oxygen radicals (hydroxyl and superoxide), but also include some other molecular oxygen ($O_2$) derivatives that are non-radical, such as hydrogen peroxide ($H_2O_2$) [19]. Therefore, various types of ROS have been reported: lipid peroxide ($LO_2$) which possess no unpaired electrons, hydroxyl ($OH^-$), peroxyl (ROO$^-$), superoxide ($O_2^-$), alkoxy (RO) radicals, radicals of nitric oxide (NO), nitrogen dioxide (NO$_2$), peroxynitrite (ONOO$^-$), ozone (O$_3$), and perhaps singlet oxygen [2]. Even though lipid peroxide and hydrogen peroxide are exempted from the free radical list, they serve as reservoirs for peroxyl, hydroxyl and alkoxy radicals, which are very reactive. ROS are continually produced in living cells throughout life via two major pathways, which are characterized by their endogenous and/or exogenous origin(s).

2.2.1 Endogenous sources

Endogenous formation entails the production of ROS within the living organism due to cellular activities. Several enzyme groups have been implicated in catalyzing this process. The seven isoforms of the expanding family of transmembrane NADPH oxidases (NOXs), a superoxide-generating system, is a good example of such enzymes [20, 21]. There are various endogenous sources of ROS in the cell; however, the most relevant and extensive are the mitochondria, endoplasmic reticulum, and peroxisomes. In the electron transport chain (ETC), there are two major sites in which the generation of mitochondrial superoxide radicals take place, Complex I (NADH dehydrogenase) and Complex III (ubiquinone-cytochrome c reductase) [2, 22]. About 1–2% of consumed oxygen molecules are converted into superoxide anions at these two sites [23, 24]. In the endoplasmic reticulum, which is a lipid and protein biosynthesizing organelle, there are two main mechanisms responsible for ROS generation [25]. The initial process is the generation of ROS as a by-product during electron transfer to molecular oxygen from protein thiol structures, which is associated with protein disulfide-isomerase (PDI) and endoplasmic reticulum oxidoreductin-1 (ERO-1) [19, 25]. The other procedure entails ROS production during protein misfolding as a result of depletion of glutathione (GSH) [26, 27], this is followed by reparation of thiols thereby permitting their interaction with ERO-1/PDI and their re-oxidation [25]. The process leads to cycles of formation and breakage of disulfide bonds, and each cycle generates more ROS as a by-product [28]. Finally, in the peroxisome, ROS production takes place in diverse metabolic pathways including fatty acid $\alpha$- and $\beta$-oxidation, phospholipid biosynthesis, polyamine oxidation, amino acid catabolism, and glyoxylate metabolism. Perhaps most importantly, the oxidative phase of the pentose phosphate pathway [29] functions through the activity of a diverse set of enzymes that generate several types of ROS, such as hydrogen peroxide, hydroxyl radical, superoxide, nitric oxide radicals and peroxynitrates, as part of their physiological functions [30].
2.2.2 Exogenous sources

ROS production can be prompted by a number of external/environmental factors. These include ultraviolet light, narcotic drugs, chemicals, and pollutants (in food and air) [31, 32]. When cells are exposed to radiation, it in turn leads to the production of various radical and non-radical species from ionization of intracellular water, including aqueous electrons, $\text{H}_2\text{O}_2$, and $\text{OH}^-$ [19]. Air pollutants such as cigarette smoke, motor vehicle exhaust and industrial contaminants encompassing many types of NO derivatives comprise the main sources of ROS that affect and cause organism injury, either by direct contact with the skin or inhalation. Additionally, chemicals (e.g. paraquat) that react to form either peroxides, ozone or superoxide, and a number of drugs, such as bleomycin and adriamycin, whose mechanism of action is mediated through the generation of ROS, are also primary sources of ROS [13, 19, 33, 34]. Most notably, it is important to emphasize the fact that food is considered the most relevant source of oxidants [19]. A large proportion of consumed food is oxidized to a high extent and contain varieties of oxidants such as peroxides, oxidized fatty acids, transition metals and aldehydes. These oxidative compounds that are taken into the intestinal tract cause great oxidative pressure on the intestinal mucosa [33].

2.3 Physiological roles of ROS

Although ROS are considered detrimental to health when excessive in the body system, they also play a series of vital roles in human physiology [35]. ROS have been shown to regulate the diameter of blood vessels, where ROS from the mitochondria (specifically superoxide and hydrogen peroxide) facilitate physiological reaction to factors including shear-stress in human coronary arteries [36, 37]. Another physiologic role is their facilitation of oxygen sensing in the body [35] which is essential to cellular health due to the fact that it permits cells to initiate adaptive responses which will in turn increase the survival probability in anticipation of limited oxygen availability. The ETC in the mitochondria also acts as an oxygen sensor by producing more ROS in response to limited oxygen supply (hypoxia) [38]. Other important roles include maintenance of genomic stability and regulation of activities of the skeletal muscle [39–41]. ROS are also critical for the immune system, where the presence of pathogens results in elevated ROS generation which further results in the release of phagocytes that serve as a first defense mechanism [42].

2.4 Antioxidants

Antioxidants are the organism’s means of defense against the destructive effects of ROS production and accumulation [43]. The exposure of living cells to the harmful effects of free radicals triggers reactions that activate multiple internal defense mechanisms, which helps the body in the removal of free radicals and their derivatives [44, 45]. Antioxidants engage in three major functions: preventing, repairing, and deactivating the detrimental effects of ROS [46]. Generally, antioxidants in living cells can be classified into two primary groups based on their mode of action on the ROS, enzymatic and non-enzymatic antioxidants [45].
2.4.1 Enzymatic antioxidants

Enzymatic antioxidants are antioxidants that function in the break-down and removal of free radicals. These are enzymes that convert harmful oxidative products to hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) and then to water in a multi-step reaction where copper, zinc, manganese, and iron are obligatory cofactors [47]. Examples of enzymatic antioxidants are superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), glutathione reductase (GR) and peroxiredoxins (Prxs) [45], which must function in concert to exert the intended antioxidant effects. SOD is particularly significant as it has the ability to catalyze the reaction that turns superoxide anion into hydrogen peroxide and molecular oxygen, which is a very relevant first line defense against ROS activity [48].

2.4.2 Non-enzymatic antioxidants

Non-enzymatic antioxidants are those that function by interrupting ROS chain reactions [47]. Few examples are vitamin E, vitamin C, carotenoids, plant polyphenol, ceruloplasmin, ferritin, thiols (e.g., glutathione) and albumin [45, 48]. Vitamin E act on cell membrane to prevent the generation of free oxygen radicals, Vitamin C prevents oxidative stress through mobbing of free oxygen radicals by neutralizing lipid hydroperoxyl radical depending of vitamin E driven mechanism and preserving proteins from alkylation through electrophilic lipid peroxidation by-products [45]. Plant polyphenols nullifying free radicals through donating of an electron or hydrogen atom [47].

3. Oxidative stress and male reproductive cells

3.1 Origin of ROS in the male reproductive system

There are different types of cells in human semen which include mature and immature sperms, leukocytes, round cells from diverse spermatogenic process stages and epithelial cells [8]. Of the aforementioned cells, the major sources of ROS are immature sperm cells and leukocytes [49]. Excessive ROS production has been reported to be associated with leukocytes (especially macrophages and neutrophils), eventually causing sperm dysfunction [8]. Reports have also shown that a positive association exists between immature sperm cells and the production of ROS. This effect may have a negative effect on ejaculate quality. Also the increase of immature sperm cells in semen is directly proportional to greater concentration of mature sperm cells with damaged DNA [50].

Apart from the aforementioned endogenous ROS sources in the reproductive system, male reproductive organs are exposed to many exogenous sources of oxidants including those derived from individual lifestyle such as alcohol use, smoking, obesity, and poor dietary intake [8]. Environmental sources of ROS include pollution, exposure to heavy metals, phthalate, heat and mobile phone radiation [8]. ROS can also affect the male reproductive system through genitourinary tract infections or could be iatrogenic through exposure to drugs, or due to clinical varicocele [8]. The role of OS in male fertility is summarized in Figure 1.
3.2 Oxidative stress and spermatogenesis

Spermatogenesis involves proliferation of spermatogonia, spermatocytes meiosis and spermiogenesis occurring in the seminiferous tubules located in the testis [13]. The process is extremely replicable generating about one thousand sperm cell per second. The illustration of the process involves mitotic division of spermatogonia giving rise to spermatocytes which go through meiosis and give rise to haploid cells known as spermatids that are finally transformed by spermiation to spermatozoa [51]. When there is a disturbance in this process it can result in male infertility. One of the factors that can disrupt the process of spermatogenesis is oxidative stress [13]. Approximately, ROS contributes to about 30–80 percent of male infertility and male gametes activities are altered by oxidative stress [8].

The oxidative stress caused as a result of free radicals have a significant impact in the production as well as increasing abnormal spermatozoa, decreasing spermatozoa count and promoting sperm DNA transformation and fragmentation [52–55]. That the greater susceptibility of spermatozoa to oxidative stress when likened to other cells is owing to the fact that mature sperm cell have cytoplasm in limited amount, the sperm structure having greater level of unsaturated fatty acids and the antioxidant in sperm cells are being suppressed by ROS concentration [56]. Oxidative stress can also result in arterial occlusion then severe damage to the cell of the reproductive system and as a result defects in spermatogenesis occurs [55].

3.2.1 The antioxidant system in semen

Semen antioxidant system consist of enzymatic and non-enzymatic factors and compounds with low molecular weight having antioxidant capacity acting upon one another to bring about protection against ROS [57]. It has been reported that if any of these is inadequate it may lead to total plasma antioxidant capacity reduction [57]. Three essential antioxidant enzyme in the semen are catalase, superoxide dismutase
and glutathione peroxide [57]. Superoxide dismutase (superoxide oxidoreductases – SOD) which are metaloenzymes capable of catalyzing superoxide anion dismutation reactions they are of two forms—intracellular and extracellular [58]. The intracellular forms includes copper- zinc SOD having in the active center copper and zinc (Cu, ZnSOD, SOD–1) which is found mainly in the cytoplasm, and manganese SOD found majorly in the mitochondrial matrix and having in its active center manganese (MnSOD, SOD–2). Acting in the extracellular space is the extracellular form of SOD (EC–SOD, SOD–3) and it is associated with the surface polysaccharides and can be found free, they have an active center made of copper and zinc [59].

Catalase catalyzes the reaction in which hydrogen peroxide is decomposed to molecular oxygen and water. Having a heme system structure with centrally located iron atom. It can be present in human as well as rat spermatozoa and seminal fluid having the prostrate as its source [58], and it enhances nitric oxide induced capacitation [57]. Also present as antioxidant system in the semen is the enzyme glutathione peroxidase (GPX), GPX has the capability of catalyzing organic peroxides, hydrogen peroxide as well as peroxides of phospholipids reduction [59].

3.2.2 Tests to measure reactive oxygen species in semen

Various tests which have been classified into direct and indirect assay are used in the determination of seminal ROS levels [60]. Report has shown hyperviscosity to be suggestive of oxidative stress due to its association with elevated malondialdehyde levels [60]. Factor such as increase in round cells or leukocytes being a respectable source of ROS may infer OS and abnormal sperm morphology [61]. Tests such as hypo-osmotic swelling indicate spermatozoa membrane damage as a result of lipid peroxidation therefore indicating greater ROS level in semen [62].

3.3 The effect of oxidative stress in steroidogenesis

So as to elucidate the role of oxidative stress in steroidogenesis, a number of studies have been done on animal models through introduction of exogenous sources of oxidants. ROS can impair steroidogenesis through destruction of important components in the steroidogenic pathway [63]. In another animal study, steroidogenesis, as implied by the level of FSH, LH and testosterone was seen to be reduced in animals fed with selenium-deficient diet when compared with selenium-fed animals. This indicate a possible role of oxidative stress on steroidogenesis in selenium deficient animals through the ability of selenium as an antioxidant to reverse this reduction in steroidogenesis [64]. Also increase in oxidative stress may result in gonadal dysfunction, reduction in testosterone level and testicular tissue damage indicating that gonadal steroid biosynthesis can be affected by oxidative stress [64]. In a lipopolysaccharide induced oxidative stress model in rats, it was reported that a correlation exists between a progressive oxidative state and reduction in the steroidogenic acute regulatory protein [65].

3.4 Oxidative stress and its effect on intercourse (erectile dysfunction)

Reasonably sufficient erectile and sexual functionality is essential for men [66]. Sexual activities improve the quality of life in men and promote longevity [67]. It has been reported that erectile dysfunction (ED) is a major challenge in men, which is estimated to be encountered by 40% of ≥40-year-old males [67]. ED can develop due to psychological, endocrine, vascular, neurological, and immune factors acquired
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via environmental exposure, lifestyle and underlying pathology [68]. The regular final mechanism of ED is vascular failure of the penis driven by significant corporal smooth muscle dysfunction which is mediated and skyrocketed via intracellular oxidative stress cumulating in a rise in smooth and endothelial muscle cell dysfunction with increase in the rate of apoptosis [67]. Nitric oxide (NO) is essential for adequate erection via nitric oxide synthase transcription (NOS) to bring about vasodilation as well as penile engorgement with blood [68]. On this basis the regular vascular failure mediator in ED is inflammation and OS, this it does through NOS reduction and subsequent reduction in NO [68]. Dysfunctional endothelial cells and increase in cellular adhesion molecules caused by inflammation enhance local arteriosclerosis and hardening of the vasculature which in turn result in local inflammation and OS [68].

3.5 Role of antioxidants in reversing oxidative stress-induced infertility in males

Genetic structure and metabolic process can influence the body’s ability to produce antioxidants which has capacity to impede the effect of oxidative stress. Other factors such as pollutant, diet and chemicals can also contribute to a marked reduction in the body’s antioxidant capacity [55]. Therefore, there is need for the introduction of exogenous antioxidant to supplement the antioxidant defense in the body [55]. Therefore, the following are some of the factors reported to be free radicals scavengers and efficient antioxidants capable of reducing testicular oxidative stress [55].

3.5.1 Vitamin C and vitamin E

Vitamin E also called α-tocopherol is an effective lipophilic antioxidant which maintains and protects spermatozoa and also contributes to the liveliness of spermatocytes and sertoli cell lines [55]. Vitamin C also called ascorbic acid plays vital role in spermatogenesis. For this reason, inadequacies in either of these two vitamins result in testicular oxidative stress and disorders of spermatogenesis and testosterone production [69]. Furthermore, vitamins C and E therapies combat oxidative stress induced by cadmium, alcohol, endosulfan and arsenic and also bring about a reduction in resultant complications [70]. Vitamin E has the ability of attenuating lipid peroxidation in mitochondrial and testicular microsomes and also able to combat adverse effects of oxidative stress that occur as a result of exposure to some exogenous factors such as iron overload, ozone gas, aflatoxin and ozone gas thereby being effectual in the protection of testicular functions [71].

3.5.2 Zinc

Zinc has been reported to be an effective antioxidant agent as well as major constituent of free radical-inhibiting enzymes like SOD [55]. Also, zinc through transferring and relocation of metals such as copper and iron is capable of preventing lipid peroxidation [72]. Studies have shown a reduction in antioxidant defense potential and a synchronous elevation in lipid peroxidation in testicular tissue in rats fed with zinc-deficient diet [70].

3.5.3 Selenium

Selenium is an important integrant of selenoproteins, it is essential in preventing OS, maintaining redox signaling state in cells and regulating thyroxine metabolism [55].
This antioxidant prevents oxidative stress by reducing free radical population in the male reproductive cells and fluids [55]. It also protect some indispensable vitamins like vitamin C and vitamin E in the body by acting synergistically with them thereby decreasing damages induced by free radicals to reproductive cells [55].

4. Effect of oxidative stress on female reproductive function

4.1 Effect of oxidative stress on folliculogenesis

It has been reported that increase in the levels ROS is related with reduction in the reproductive capability in females and infertility [73]. Reports have also shown that an elevation in the production of steroid hormone by developing follicles goes along with an increase in cytochrome P450 activity which results from the production of ROS such as hydrogen peroxide [74].

DNA damage and ovarian follicle apoptosis may be caused also by OS [75, 76]. It was noted that in dominant follicles that there is a simultaneous increase in estrogen and catalase in reaction to FSH stimulation which suggests a role of catalase in apoptosis prevention among follicles [77]. It was also reported that the oxidized form of LDL (oxLDL) and its receptor (LOX-1) are bestowed in follicular fluid or human granulosa cells and are elevated in oxidative stress states interfering with follicular maturation [78].

Growing follicles may be an inadvertent target of ROS especially in patients undergoing radiotherapy which generate a high amount of ROS [79, 80]. The ROS produced in granulosa cells may have a negative impact on oocyte fertilization as well as the rate and quality of implantation of the embryo [80]. Reports have also proven that germ cells are more vulnerable to deleterious effect of OS than somatic cells [81, 82]. Furthermore, reports has shown that OS from radiotherapy may result in ovarian atrophy, oocyte loss coupled with reduction in follicle store which may in turn result in menstrual irregularities, ovarian failure and ultimately infertility [80].

4.2 Effect of oxidative stress on steroidogenesis in females

When the ovary is over-exposed to hydrogen peroxide, it uncouples the LH receptor from adenylate cyclase. This causes disruption in protein synthesis and utilization of cholesterol by the mitochondrion p450 side chain cleavage [83]. This disruption is likely facilitated by the reduced production of steroidogenic acute regulatory protein (StAR). The StAR enhance the movement of cholesterol to the inner membrane of the mitochondria where p450 side chain cleavage converts cholesterol to pregnenolone [83]. Also, a reverse transport of cholesterol and estrogen synthesis in the follicle is facilitated by Lecithin cholesterol acyltransferase (LCAT). Evidences exist that suggest that these transporters are subjects of oxidative stress. A study reported that exogenous antioxidants like vitamin C are accumulated in mature follicles to prevent LCAT from oxidative damage and for steroidogenesis enhancement [84].

4.3 The effect of oxidative stress on ovulation

Ovulation is a process involving local inflammatory response, which leads to elevated levels of ROS [85]. The increased ROS levels may lead to potential destruction of the granulosa cells which are going through luteinization in the course of ovulation.
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ROS are generated during ovulation in a similar way as it occurs in inflammation. It was reported that agents that inhibits inflammatory response also suppresses ovulation [87]. The source of ROS in this process seems to be from macrophages and neutrophils because they are common in the ovaries and they led to increase production of free radicals [88]. ROS has been shown to be generated during the ovulatory cascade. ROS in ovulation was noted to be mediated by protein kinase C and gonadotropin leading to production of nicotinamide adenine dinucleotide phosphate oxidase which engenders more reactive species in the course of ovulation [89].

4.4 Oxidative stress and its impact on artificial reproductive techniques (ARTs)

ARTs are advanced technological procedures which are used to treat infertility [90]. The quality of oocyte is greatly dependent on the follicular fluid microenvironment, thereby affecting the fertilization and embryo rate and quality respectively [73]. Oxidative stress markers has being said to be present in the follicular fluid of patient undertaking embryo transfer (ET) or even in-vitro fertilization (IVF) [91–94]. A reduction in intra-follicular oxygenation is said to be interrelated with a reduction in the potential of oocyte development this is as a result of an increase in the frequency of oocyte cytoplasmic disorder, impairment in cleavage and abnormal segregation in oocyte chromosome caused by follicles that are poorly vascularized [8]. The increase in embryo fragmentation, which leads to an increase in apoptosis, has been reported to be caused by ROS [8]. Hence, elevation in the ROS level is detrimental to the growth of the embryo and Sperm-oocyte interaction [8].

4.5 Role of oxidative stress in pathological pregnancies

Pathological pregnancies such as pre-eclampsia have been reported to be a complicated multisystem disorder affecting about 5–8 percent of all pregnancies and it contributes largely to fetal and maternal mortality and morbidity [95]. It has been reported that etiopathogenesis of preeclampsia may be caused by of oxidative stress and may be due to an elevation in the placenta metabolic activity as well as a reduction in its antioxidants scavenging power [95]. The role of oxidative stress in the female reproductive processes is summarized in Figure 2.

4.6 Role of antioxidants in reversing the effects of oxidative stress and infertility in females

Reports have shown that the female reproductive system is susceptible to oxidative damage which if left untreated the damage process continues [8, 95]. There are various antioxidants that have been reported to scavenge free radicals and to keep the reproductive system healthy [96]. They include vitamins C, E and β-carotene, L-carnitine, acetyl L-carnitine and also metallo-enzymes such as catalase, superoxide dismutase (SOD, containing copper, manganese and zinc), glutathione peroxidase (GPx, containing selenium) and superoxide dismutase (SOD, containing manganese, copper and zinc) [96].

The antioxidants mentioned above when taken helps the total antioxidant system to be coordinated functionally [97]. Antioxidant system in the ovary such as carotenoids, CAT, glutathione and vitamin E) are responsible for regulation of ROS [96]. It was documented that the effect of SOD is noticeable in the theca interna cells of antral follicles [96]. These cells during maturation phase protect oocyte from been
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destroyed by redundant ROS [96]. Vitamin C which can be found in the cytosol of oocyte and extracellular fluid is used in the treatment of luteal phase disorder and recurrent abortions [8]. Vitamin C is given to patient during in vitro fertilization (IVF) embryo transfer as a supplement in hormonal stimulation to guarantee a large concentration of vitamin C in the follicular fluid which improved oocytes and embryo qualities.

4.7 Role of oxidative stress in embryo and fetal function

During of embryonic development, the embryo is vulnerable to OS [97]. The stage of one-cell embryo depends on Krebs cycle during early phases of development, on the other hand during the other initial embryo organogenesis, anaerobic pathway and glycolysis is relied on, so does blastocyst [97]. However, there is a larger dependence on aerobic and oxidative metabolism at the establishment of circulatory system leading to a higher production of ROS by the mitochondria but antioxidants are present as well to negate and detoxify ROS [95]. But with time there may be disruption in the antioxidant and oxidant balance by the exogenous agents responsible for the stimulation of ROS which results in disruption in embryo and fetal functions [97].

5. Conclusions

Oxidative stress plays a notable role along the several processes involved in male and female reproduction. While a physiologic amount of reactive species are needed for optimal functioning of the male and female sex organs there are conditions which produces a considerable amount of reactive species and a concomitant depression of
the antioxidant system. This oxidative stress state impairs the reproductive processes and causes general disruption through inflammation, DNA damage, lipid peroxidation, protein alterations and mitochondrial dysfunction. It will be of importance to identify oxidative stress biomarkers specific for each reproductive processes and map out their standard range so as to advance measures to curtail the growing level of infertility among human population in future research. It is also recommended that the role of genetics and oxidative stress in the etiology of infertility should be a priority for researchers.

Conflict of interest

‘The Authors declare that there is no conflict of interest’

Abbreviations

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<tr>
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<tr>
<td>ARTs</td>
<td>Artificial Reproductive Techniques</td>
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<tr>
<td>CAT</td>
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<td>CuSOD</td>
<td>Copper containing superoxide dismutase</td>
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<td>DNA</td>
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<td>EC–SOD or SOD–3</td>
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PDI  Protein disulfide-isomerase
Prxs  Peroxiredoxins
RO  alkoxy
ROO’  Peroxyl
ROS  Reactive Oxygen Species
SOD  Superoxide Dismutase
SOD–1  Copper Zinc superoxide dismutase
StAR  Steroidogenic acute regulatory protein
ZnSOD  Zinc containing superoxide dismutase

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