12 Pathological Role of Reactive Oxygen Species on Female Reproduction

Lisa Goutami, Soumya Ranjan Jena, Amrita Swain, and Luna Samanta

Abstract

Oxidative stress (OS), a clinical predicament characterized by a shift in homeostatic imbalance among prooxidant molecules embracing reactive oxygen species (ROS) and reactive nitrogen species (RNS), along with antioxidant defenses, has been established to play an indispensable part in the pathophysiology of subfertility in both human males and females. ROS are highly reactive oxidizing by-products generated during critical oxygen-consuming processes or aerobic metabolism. A healthy body system has its own course of action to maintain the equilibrium between prooxidants and antioxidants with an efficient defense system to fight against ROS. But when ROS production crosses its threshold, the disturbance in homeostatic balance results in OS. Besides their noxious effects, literature studies have depicted that controlled and adequate ROS concentrations exert physiologic functions, especially that gynecologic OS is an important mediator of conception in females. Yet the impact of ROS on oocytes and reproductive functions still needs a strong attestation for further analysis because the disruption in prooxidant and antioxidant balance leads to abrupt ROS generation initiating multiple reproductive diseases such as polycystic ovary syndrome (PCOS), endometriosis, and unexplained infertility in addition to other impediments in pregnancy such as recurrent pregnancy loss, spontaneous abortion, and preeclampsia. The current article elucidates the skeptical state of affairs created by ROS that influences female fertility.

Keywords

ROS · RNS · Polycystic ovary syndrome (PCOS) · Endometriosis

12.1 Introduction

Elevation in reactive oxygen species (ROS) level is an emerging health concern during aging and also in several other diseases in both humans and animals. High ROS concentration can also be the reason for increasing oxidative stress (OS) or decreasing efficiency of antioxidant system. It acts like a double-edged sword for its involve-

L. Goutami · S. R. Jena · L. Samanta (✉)
Department of Zoology, Redox Biology & Proteomics Laboratory, School of Life Sciences and Centre for Excellence in Environment and Public Health, Ravenshaw University, Cuttack, Odisha, India
e-mail: lsamanta@ravenshawuniversity.ac.in

A. Swain
Department of Zoology, Biochemistry & Molecular Biology Laboratory, School of Life Sciences, Bhubaneswar, Odisha, India

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ment in physiological processes as a major signaling molecule and also plays a role in pathological processes like fertility and reproduction, maturation and fertilization of oocyte, development of the embryo, and maintaining pregnancy. Several studies have reported that age-related decline in fertility is due to the modulation of OS. It is also reported to play a role in normal parturition and initiation of preterm labor. It is found that antioxidants can prevent from damage to ovulation-induced OS and also disruption of DNA of the ovarian epithelium. Growing evidences support that OS has effect on pathophysiology of female reproduction like free radical-induced birth impairment, pre-eclampsia, hydatidiform mole, and other situations such as abortions (Agarwal et al. 2008, 2012). Studies reveal that OS also has a pathophysiological role in infertility and assisted fertility. Moderate concentration of ROS is also involved in growth and apoptotic protection signal transduction. Increased ROS levels alter macromolecules like proteins, lipids, and nucleic acids that significantly damage the cellular structure and further lead to OS. Cells have the capability to escape the damage caused due to ROS by the presence of its nonenzymatic antioxidants like glutathione, vitamin C, and vitamin E and enzymatic antioxidants like superoxide dismutase (Mn-SOD and Cu/Zn SOD) that helps in conversion of superoxide to hydrogen peroxide, glutathione peroxidase, and catalase which neutralize the hydrogen peroxide. Complex interaction among prooxidants and antioxidants ensures the maintenance of intracellular homeostasis of ROS in female reproduction (Fujimura et al. 2000). The present study addresses the main pathophysiology caused by ROS in the female reproductive system.

12.2 Pathological Effect of ROS on Female Reproductive System

ROS and its scavenging system play an important role in reproductive physiology. Reports confirmed the existence of ROS and different antioxidant enzyme transcripts in the female reproductive tract (Sugino 2005; Agarwal et al. 2008). If ROS are kept in adequate concentration in the reproductive apparatus, it acts as an important mediator in steroidogenesis in the ovary, hormone signaling, ovulation, formation of the corpus luteum, luteolysis, oocyte maturation, luteal maintenance in pregnancy, implantation, compaction, blastocyst development, and germ cell function. It is also observed that intermittent ROS generation occurs inside the ovary as a physiological by-product during follicular and luteal phases (González et al. 2006). Macrophages and neutrophils are considered as other sources of ovarian ROS, and its presence is well documented in both corpora lutea and follicles (Nakamura and Sakamoto 2001).

12.2.1 Reduced Growth and Development of Oocyte

Stress is a significant component that affects a healthy person's physical and emotional well-being, disrupting the body homeostasis. The foremost reason of psychological stress is a change in one's lifestyle. Psychological stress may have an effect on female reproduction biology by affecting the follicle, ovary, and oocyte. Increased stress hormone level, such as cortisol, limits estradiol synthesis within the follicle with modifications in the granulosa cell functions, resulting in poor oocyte quality. Modern lifestyle changes can affect female reproduction by production of ROS in the ovary. Neutralization of ROS and balancing antioxidant enzymes concentration are a prior requirement of the ovary for maintaining female reproductive health. The ROS generation at the basal level is necessary for regulation of oocyte activities, but excessive accumulation can be the reason of OS (Agarwal et al. 2012).

The major causes that induce ROS accumulation can be environmental and lifestyle changes, pathological conditions, or drug treatment, which imparts negative effect on oocyte physiology by promoting apoptosis which can lead to OS (Tripathi et al. 2011; Sharma et al.

2013). Apoptosis of granulosa cells triggered by OS leads to reduction in levels of estradiol 17ß, quality of oocyte, and rate of ovulation (Tripathi et al. 2013). A recent report suggested that granulosa cell apoptosis by ROS lowers the granulosa cell-oocyte communication, which impacts nutrition availability and decreases the quality of preovulatory oocytes (Chaube et al. 2014). Furthermore, OS induces disorders in chromosomal segregation, telomere shortening, oocyte fragmentation, and failed fertilization resulting in age-related fertility decline (Ishii et al. 2014; Tatone et al. 2015). High ROS level (beyond physiological range) may trigger mitochondria-mediated cell cycle arrest by maturation-promoting factor (MPF) destabilization and apoptosis in oocyte (Tiwari et al. 2016). An in vitro study defended the probability of transitory increase in intracellular ROS facilitating resumption of meiosis from diplotene arrest, while further enhancement caused OS leading to arrest in cell cycle followed by apoptosis (Chaube et al. 2005; Tripathi et al. 2009). Similar reports explain rise in ROS level triggering cell cycle arrest in embryos of humans and mice (Tripathi et al. 2009). Despite the fact that immature and mature oocytes both encounter cell cycle arrest and cell death induced by OS. Although, immature oocytes are more prone to OS-mediated morphological alterations by apoptosis like membrane blebbing, cytoplasmic granulation, shrinkage, and degeneration (Men et al. 2003; Chaube et al. 2005). Another study suggested that frequent stimulation of exogenous gonadotropin hormone also induces ovarian OS and ovulation of poor-quality oocytes with reduced growth (Chao et al. 2005). Oocyte apoptosis is facilitated both by death receptor and mitochondria-mediated pathways. Especially OS-induced mitochondrial caspase-mediated pathway takes an important part in eliminating germ cells from the ovarian cohort which have the capability to impair oocyte quality even after ovulation (Tiwari et al. 2016).

12.2.2 Ovarian Steroidogenesis

ROS are the preordained end product of normal aerobic metabolism, and hence, steroidogenic cells can be served as one of the primary sources of ROS. Some other potential intracellular sources of ROS are endoplasmic reticulum, plasma membrane, and electron transport systems of mitochondria and nuclear membrane (Freeman and Crapo 1982). Evidence suggested that there is a substantial correlation between Cu, Zn-SOD, and progesterone concentrations in serum. However, the amount of lipid peroxide rose during the regression phase in the corpus luteum in rat models and showed an opposing trend in progesterone concentration from serum (Sugino et al. 1993; Shimamura et al. 1995). At the time of steroidogenesis, ROS production is normal to restrict the corpus luteum capability for progesterone synthesis (Carlson et al. 1995). During pregnancy, a decrease in the expression of Zn-SOD and Cu-SOD leads to a rise in ROS, which inhibits progesterone production. Therefore, an increase in the capability to scavenge ROS could be linked to the preservations of the integrity of luteal cells and a longer corpus luteum lifespan (Sawada and Carlson 1996). Repoport et al. depicted that progesterone synthesis in the corpus luteum is associated with SOD and catalase in other mammals, such as bovines (Rapoport et al. 1998). It is possible that luteotropic chemicals, which are generally produced by the placental cells during pregnancy, induce the expression of luteal cells protecting molecules from ROS. Finally, placental luteotropins enhance Zn-SOD and Cu, which is a key mechanism for rescuing the corpus luteum and maintaining progesterone synthesis (Behrman et al. 2001). During follicular growth, where superoxide radicals are produced through normal metabolism and steroidogenesis in mitochondria and cytosol, there it also bears the major role among ROS to inhibit steroidogenesis. Cu, Mn-SOD, and Zn-SODs act as scavengers of superoxide radicals and protectors of

granulosa cells and theca interna cells that significantly facilitate steroidogenesis and follicular growth. On the other hand, a unique hypothesis explains that Cu, Zn-SOD may have a role in progesterone biosynthesis by theca interna cells.

12.2.3 Ovulation

The ovulation mechanism has been compared to an inflammatory response (Espey 1980; Behrman et al. 1996). The major factors involved in inflammation during ovulation process are higher level of prostaglandin and cytokine production, along with the proteolytic enzymatic action and enhanced vascular absorptivity (Brannstrom 2004). ROS may act as a significant inflammatory response mediator, and therefore these have been described to be associated with ovulation. Sato et al. demonstrated that in pregnant mare serum gonadotropin-human chorionic gonadotropin (PMSG-HCG) rats, intravenous injection of SOD suppressed the ovulation during in vivo condition (Sato et al. 1992). Using a perfused in vitro ovary model, Miyazaki et al. also reported that ovulation is inhibited in rabbit upon SOD administration stimulated by HCG. In fact, after HCG injection, raised lipid peroxide concentration is the result of ROS in the ovary of rat (Miyazaki et al. 1991). Therefore, these observations strongly indicate that ROS are involved in the rupturing process of the follicle. As per in vitro reports, the perfused ovary also encounters SOD averted ovulation, revealing that ROS sources are localized in the ovary. Residential leukocytes or endothelial cells swarm around preovulatory follicles, infiltrating the granulosa cell layer and that could be the source of ROS during the ovulatory process (Araki et al. 1996). Kodaman and Behrman reported that ROS are generated from isolated follicles (Kodaman and Behrman 2001). According to Shirai et al., the polymorphonuclear leukocytes in the peripheral circulation secrete LH from the LH receptors present in it and also increase superoxide radical generation (Shirai et al. 2002). Administration upon monoclonal antibody (Mab) depleting neutrophil results in reduction in rate of ovulation in rats (Brännström et al. 1995; Kodaman and Behrman 2001). When the effect is compared to SOD alone about the ROS species, these factors, like parallel administration of catalase and hydrogen peroxide catalysis, impart no additional effect on the ovulation rate (Miyazaki et al. 1991). Moreover, SOD can fully inhibit ROS generated by follicular cells, but catalase could not do the same (Kodaman and Behrman 2001). These findings divulge that superoxide radical is the radical species involved in ovulation.

12.2.4 Formation of Blastocysts

Blastocysts, like every other actively metabolizing cell in the body, produce ROS. Basically, three enzyme systems regulate ROS production: oxidative phosphorylation, xanthine oxidase, and NADPH oxidase system (Guerin et al. 2001). Participation of other oxidase enzymes in the production of ATP consequently elevates the ROS levels. As demonstrated in rabbit blastocysts 4/5 days after coitus, the embryos can produce O_2, H_2O_2, and OH (Manes and Lai 1995). ROS concentrations have decreased in in vivo culture as compared to in vitro culture in mice. The amount of ROS produced varies depending on the stage of embryo development. ROS is manufactured twice in mouse embryos during the period of fertilization and the G2 or M stage of the second cell cycle (Nasr-Esfahani et al. 1990; Nasr-Esfahani and Johnson 1991). Another study showed that mitochondrion is not the only source of ROS production. In rabbit blastocysts, Manes and Lai (1995) found that cyanide is an irreversible mitochondrial respiration blocker that did not decrease ROS production and suggested that, aside from oxygen metabolism, there are other sources of oxygen radical generation. The NADPH oxidase is another oxidizing system discovered in the preimplantation embryo. As seen in rabbit blastocysts, the NADPH oxidase system can also yield free radicals (Manes and Lai 1995). In two-cell mouse embryos, suppressing the NADPH oxidase system blocks the production of H_2O_2 (Nasr-Esfahani and Johnson 1991). It is

necessary to investigate whether a comparable system in the human embryo exists or not and whether it is responsible for the developmental arrests of embryos.

12.2.5 Implantation

After fertilization, the blastocyst development of the embryo includes ICM (inner cell mass) and trophectoderm stage differentiation which infers cleavage, quick cell division, and compaction (Paria and Dey 1990; Iwata et al. 2014). Cell division in preimplantation of embryos occurs in a quick and regulated manner that demands great energy, through ATP during oxidative phosphorylation in mitochondria, and also produces ROS, namely, H_2O_2. The hydroxyl radical (OH^-) of Fenton reactions is engaged in the production of H_2O_2. In typical conditions, H_2O_2 participates in the mitochondrial respiratory chain. The enzymatic defense system comprises of metalloenzymes such as SOD and catalase (CAT) (Guerin et al. 2001; Dumollard et al. 2007; Levine and Puzio-Kuter 2010; Silva et al. 2010; Migdal and Serres 2011). In mammalian cells, there is a distinct secretory mechanism of H_2O_2. It is manufactured as a consequence of numerous oxidative reactions like peroxisomal enzyme activities, oxidative protein folding, and respiratory chain cascade in the ER. Neutrophils give rise to H_2O_2, which functions adversely to microbial contamination. However, concern is toward its secondary messenger aspect in the course of proliferation and differentiation of the cell (Rhee et al. 2005; Rhee 2006). The transcription factor, hypoxia-inducible factor-1 (HIF-1), is activated and managed by H_2O_2. Numerous growth factors like insulin-like growth factor-1 (IGF-1) and IGF-2 with vascular endothelial growth factor are positively regulated by this transcription factor, influencing normoxia to hypoxia (Ke and Costa 2006). In the course of implantation, the action of HIF-1 is studied to be triggered by follicle-stimulating hormone (FSH) to manifest in granulosa and endometrial cells followed by regulating target genes concerned with angiogenesis and cell survival for implantation of the embryo (Critchley et al. 2006); Ke and Costa 2006; Alam et al. 2009).

12.3 Luteolysis and Luteal Maintenance of Pregnancy

Apoptotic luteal cell death is associated with structural luteolysis as suggested by evidence (Shikone et al. 1996; Roughton et al. 1999; Carambula et al. 2002; Sugino 2005). Reports suggest that different cells are destined to apoptotic cell death due to aggregation of ROS and reduction in SOD parameters (Rothstein et al. 1994; Troy and Shelanski 1994; Greenlund et al. 1995). Exaggerated levels of ROS cause cytochrome c (cyt c) from mitochondria to discharge in the cytoplasm which results in apoptosis that in turn activates caspases in interaction with some cytosolic factors like Apaf-1 and anti-apoptotic factor like Bcl-2. The whole process of releasing cyt c and apoptosis can be inhibited through superoxide generation (Cai and Jones 1998). Daramajaran et al. reported Mn-SOD and Bax are found to express in a higher and lower levels, respectively, where Bax is an apoptotic factor, rescued by HCG in corpus luteum of rabbits and involvement of Mn-SOD in the survival of luteal cells (Dharmarajan et al. 1999). Mitochondrial superoxide radical removal is essential which is demonstrated by the death of neonatal mice that lacks above-described Mn-SOD expression (Li et al. 1995). For instance, when luteal cells get exposed to environment rich in cytokine and Mn-SOD fails to induce rapidly increased ROS production in mitochondria may cause apoptosis. Naturally, few apoptosis may be seen despite the raised ROS level during the regression phase (functional luteolysis) of corpus luteum in pregnancy or pseudopregnancy phases of rats (Takiguchi et al. 2004). It may be due to the well-maintained Mn-SOD levels throughout the ongoing luteolysis in the corpus luteum, which suggests that corpus luteum is still able to safeguard against OS (Sugino et al. 1998). Tanaka et al. reported from the result of an in vitro study

in rats the functional luteolysis inducer PGF2α, which causes apoptosis via ROS in luteal cells (Tanaka et al. 2000). However, it seems insignificant as it affects only 5% loss of viable cells. Hence, this analysis supports the inference deduced by Takiguchi et al. that even the increase in ROS level could not perform a higher level of apoptosis (Takiguchi et al. 2004).

The reason of apoptotic cell death of the regressed corpus luteum during human menstrual cycle is a result of a rise in ROS and fall in Cu, Zn-SOD expression level, where expression of Mn-SOD is consistently higher, which infers the protective ability of luteal cells against OS in mitochondria (Sugino et al. 2000). The outcome of this study opens a possible way of elevation in cytosolic ROS that triggers the reduction in cytosolic Cu, Zn-SOD which collectively facilitates apoptotic death of luteal cells of the corpus luteum in humans. According to the above explanation, Cu, Zn-SOD reduction within a physiological range, like fall in the regression state in pregnant or pseudopregnant rats or decline up to 50% by antisense oligonucleotides of Cu, Zn-SOD, cannot be considered to affect apoptotic cell death. A little depletion in Cu, Zn-SOD actions may not have been sufficient to trigger apoptosis. However, Cu, Zn-SOD activity level in the human menstrual cycle showed a 30% decline compared to the level of mid-luteal phase in the regressed corpus luteum (Sugino et al. 2000). Such a huge drop in Cu, Zn-SOD action might cause apoptosis in the cells of human corpus luteum, because as stated by Rothstein et al. 40% drop in Cu, Zn-SOD expression did not cause apoptosis, whereas a 60% decrease initiated the same in nerve cells (Rothstein et al. 1994). It may be concluded from all of these studies and other reports that apoptosis may be influenced by the ROS level generated upon the decline in the Cu, Zn-SOD level (Rothstein et al. 1994; Troy and Shelanski 1994; Fujimura et al. 2000). For example, Fujiyama et al. found that when the cytosolic release of cytochrome c was obstructed by Cu, Zn-SOD, it inhibited apoptosis in the brain of a mouse (Fujimura et al. 2000). Additionally, some other evidences depict an intimate rapport between ROS and apoptosis of luteal cells in other animals (e.g., bovines or pigs) (Murdoch 1998; Nakamura and Sakamoto 2001).

12.4 Endothelial Dysfunction in the Uterus

Oxidative stress highly impacts the physiology of pregnancy. It is instrumented by placental mitochondrial activity and ROS outcome of normal cellular activity (Roberts et al. 2009). Endogenous ROS is primarily produced by mitochondria, although some amounts are also produced by endoplasmic reticulum and peroxisomes (Snezhkina et al. 2019). Liberation of detrimental mediators into maternal circulation is brought about by excessive ROS generation. This excessive release is distinctly obvious in insufficient placentation that subsequently leads to ischemic placental microenvironment (Wu et al. 2015). Smooth muscle and endothelium are primed by immune cells like uterine natural killer cells (uNK) and macrophages for invasion. Particularly vascular infiltration process of the decidua and myometrium needs extravillous cytotrophoblast (EVCT) as a necessary part (Tannetta and Sargent 2013). Placental insufficiency is treated as an offender in obstetric complications that comprises of preeclampsia and intrauterine growth restriction (IUGR) arises when partial trophoblast invasion occurs in the maternal uterine spiral arteries (Krishna and Bhalerao 2011; Hromadnikova 2012). Conditions such as decreased placentation, OS, ischemia, inflammation, and apoptosis of the syncytiotrophoblast result from impaired utero placental blood flow (Burton et al. 2009; Mifsud and Sebire 2014). In the event of maternal obesity, the visceral adipose tissue mass elevates adipocyte dysfunction, causing increased ROS generation. The adipose and other peripheral tissues both show a raise in insulin resistance which are interrelated to this hyperbolic ROS generation (Aroor and DeMarco 2014).

Numerous vascular conditions such as matrix metalloproteinase (MMP) activation, vascular remodeling, hypertrophy of smooth muscle, and cellular apoptosis are typically the result of ROS

overflow. ROS induces IκB kinase (IKK) complex oxidation followed by nuclear factor kappa B (NF-κB) discharge that promotes transcription of different pro-inflammatory mediators of endothelial dysfunction including intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and inflammatory cytokines like tumor necrosis factor (TNF)-α and interleukin (IL)-6 (Tenório et al. 2019; Sprague and Khalil 2009). Throughout pregnancy, this interaction is aptly maintained. However, in preeclampsia and gestational diabetes mellitus (GDM), it becomes baffled (Powe et al. 2011; Pontes et al. 2015). Endothelial dysfunction in preeclampsia and GDM mainly occurs due to amplified ROS production. This causes potentially permanent vascular damage and modified endothelial phenotype, leading to serious results (Incalza et al. 2018).

12.5 Fertilization of Eggs

Raised levels of ROS lead to OS that acts as a primary cause of male and female infertility. Cell death or senescence is sourced from OS, thereby causing oxidation of biomolecules like DNA, RNA, proteins, and lipids of a cell. During in vitro fertilization (IVF), aiming for assisted reproduction, it is absolutely necessary to reduce OS. Today, we know the issues related to assisted reproductive technology and its importance to address the mechanisms and handle it. On the contrary, the advantageous function of ROS, like intracellular signaling, has become clear for fertilization.

Sperm motility and its potential fusion with an oocyte are reduced because of OS (Agarwal et al. 2008; Aitken and De Iuliis 2009). During IVF, the quantity of ROS generated from oocytes, sperm, and fertilizing processes is estimated (Ishii et al. 2005; Miesel et al. 1993). Testicular atrophy and enhanced susceptibility to heat stress occur due to inadequacy of SOD1 encoding Cu, Zn-SOD (Ishii et al. 2005). Despite the fact that no aberration is observed in male fertility, the sperm lacking SOD1 portrays less capability of fertilization owing to increased oxidation during IVF (Tsunoda et al. 2012). Contrarily, transgenic male mice demonstrating elevated level of mitochondrial Mn-SOD encoded by SOD2 were infertile for some unknown reasons (Raineri et al. 2001). High levels of SOD actions illustrate a negative relation to the motility in human spermatozoa (Aitken et al. 1996). Deficiencies in extracellular SOD3 encoding SOD fail to display any remarkable alterations of phenotype in human male reproductive system but when the former mentioned gene was transferred to the penis showed a betterment of erectile function in mature rats (Bivalacqua et al. 2005). The reason behind it is the rapid reaction of superoxide and nitric oxide to produce peroxynitrite that increases extracellular concentration of SOD in blood plasma so that the half-life of nitric oxide was extended which resulted in improved erectile function.

Somatic cells and oocytes are associated with the extremely differentiated sperm cells through their metabolism and function. Despite having low cytoplasmic content, numerous genes are expressed throughout spermatogenesis in a testis-specific method, whose roles are justified in sperm function. Although ROS affects sperm, some quantity of ROS is generated by sperm itself. Contrary to its damaging effects, sperm functions like capacitation and activation require ROS for their mechanisms (de Lamirande and O'Flaherty 2008). Sperm makes a transient attachment to the lower epithelial cells of the oviduct and swims to the site of fertilization called ampulla. Sperm surface displays cells of oviduct and lectin-like molecules which are basically carbohydrates that are intermingled for better sperm attachment. Since adhesion was altered by reductants, adherence of sperm was decided from the redox status on the external surface of the sperm (Gualtieri et al. 2009). The epithelium of the oviduct and uterus contain glutathione (GSH) reduced along with its recycling enzyme glutathione reductase. Glutathione constitutes the chief low-molecular-weight redox system (Fujii et al. 2011) which is required for fertilization, preimplantation, and development of the embryo

(Nakamura et al. 2011). As a matter of fact, many infertile patients are treated with GSH or its equivalent making the administration of GSH a promising way to enhance fertility (Irvine 1996). GSH can be supplemented for improvement in dyspermia which is a germ-free reproductive tract infection or due to varicocele. The infertile γ-glutamyl transferase knockout mice with reduced testes and seminal vesicles can reinstate entirely to their natural size of the testes upon administrating GSH or *N*-acetylcysteine compared to wild-type mice, and the mutant mice get fertile (Kumar et al. 2000).

Cells are defended from oxidative damages by antioxidative defense systems. However, several physiological functions are also portrayed by ROS such as making improvements in signals of phosphorylation by managing phosphatases (Rhee 2006). It is an established fact that extracellular $O_2^{\cdot-}$ and acrosome reaction of spermatozoa are connected. It has been suggested that both hydrogen peroxide and superoxide participate in management of this activity (de Lamirande et al. 1998). Redox reactions seemingly control the fertilizing capabilities of sperm; however, knowledge is limited about their reactions. For example, PDILT, which is the protein disulfide isomerase homolog, modulates the sperm membrane protein ADAM3 found to be needed for fertility (Tokuhiro et al. 2012). Studies suggest that PRDX is relevant and it has remarkable function in ROS signaling (Rhee 2006). Among the six parts of the PRDX group, PRDX4 holds an important role in spermatogenesis because lacking the same results in delay in sexual maturation and makes testicular cells susceptible to heat stress (Iuchi et al. 2009). PRDX4 is expressed with a testis-specific variation and may take part in the spermatogenesis (Sasagawa et al. 2001; Yim et al. 2011). Reduction in redox condition causes elevation of PRDX oxidation in the sperm, which seems to initiate male infertility (Manandhar et al. 2009; O'Flaherty and Rico de Souza 2011; Gong et al. 2012). Nevertheless, in-depth research is essential to recognize their function in reproduction.

12.6 Diseases Caused by ROS in Female Reproductive System

ROS are a double-edged sword; they serve as key signal molecules in physiological processes but also have a role in pathological processes involving the female reproductive tract. There is growing literature on the effects of ROS in the female reproduction with involvement in the pathophysiology of endometriosis, preeclampsia, hydatidiform mole, maternal diabetes, PCOS, ovarian epithelial cancer, free radical-induced birth defects, and other situations such as spontaneous abortion and recurrent pregnancy loss, intrauterine growth restriction, and fetal death.

12.6.1 Endometriosis

Endometriosis is a widespread gynecological disorder in women of reproductive age. The distinguished feature of this phenomenon is it occurs in the external tissue of the uterine cavity with prevalence of infertility and pelvic ache in patients. The primary cause of the disease is somehow indistinct and said to be founded by three main theories: retrograde menstruation, induction theory, and coelomic metaplasia. Both genomics and epigenomics are crucial for the occurrence of endometriosis with fluctuations in the reactive oxygen stress (ROS) levels and oxidative stress (OS) culminating to inflammation in the peritoneum. ROS regulates inflammatory reactions that balance cell proliferation by apoptosis. Genomic variation and cell survival are the examples of molecular modifications which are impaired parts of the pathogenesis of endometriosis. Various factors have been brought to light by latest research, which connects with oxidative stress, like cell cycle checkpoint sensors, forkhead transcription factor (FOX), hepatocyte nuclear factor (HNF), AT-rich interactive domain 1A (ARID1A), and microRNAs. FOX activity is regulated through ROS-induced post-translational modifications. FOX deprivation

wrecks the capability of cells to halt at checkpoints aiding to lesion formation, and a lower level of FOX expression in endometriosis patients compared to healthy women confirms the FOX action in the disease (Shigetomi et al. 2012). Similarly, recent studies reveal the ROS as a DNA methylation leading to aberrant gene expression. The investigation identified AT-rich interactive domain 1A (ARID1A) gene as a key factor of SWI/SNF chromatin remodeling complex, which could regulate gene expression by changing the structure of surrounding chromatin. ARID1 mutation frequency rate is found higher in cancer patients like liver cancer, breast cancer, and gastric cancer (Wu et al. 2016; Tordella et al. 2016; Jiang et al. 2015) than in endometriosis condition, yet sometimes it completely lost its expression during this clinical stage. Besides that, breast cancer only displays changes in ARID1A gene mutation frequency but does not associate with its expression level (Takeda et al. 2016). In the previous report, ROS could affect ARID1A gene expression level (Kwan et al. 2016). However, H. Xie in 2017 stated the mechanism of ROS associated with ARID1A gene silencing in endometriosis. Further experiments showed ROS regulated ARID1A gene expression by affecting its promoter methylation. HSP family includes heat shock protein 70 B as an inducible part. It occurs insignificantly under normal circumstances and gets amplified under stress. It acts as an escort for proteostatic activity like folding and translocation, with quality assurance. It is recognized to favor cell proliferation by subduing apoptosis, particularly when present in elevated concentration, as found in various tumor cells. When misfolded proteins are found in abundance, there is overexpression of HSP70, leading to a plethora of ROS. OS liberates HSP70, which instigates the function of inflammatory cytokines [93, 99] TNF-alpha, IL-1 beta, and IL-6, present in macrophages by toll-like receptors (e.g., TLR 4), perhaps being the reason of endometriotic tissue (Xie et al. 2017).

12.6.2 Preeclampsia

Human pregnancy associated with hypertension and proteinuria during the second or third trimester of gestation phase leads to preeclampsia (PE). This disease occurs among 3–8% of women worldwide, though its rate differs with geographical area, time duration in year, nutritional condition, and race/ethnicity (Steegers et al. 2010). Basically, PE occurs due to de novo hypertension (>140/90 mm Hg systolic/diastolic blood pressure) and proteinuria (>300 mg/24 h). Mostly PE gets associated with comorbidities like disseminated intravascular coagulation (DIC), edema, hepatic alterations (HELLP syndrome), and eclampsia, in particular targeting the brain (cerebral edema). PE leads to complication in the fetus like growth restriction that may lead to prematurity, loss in birth weight (1/3 of cases), and neonatal death. The disease worsens with time from its onset which may progressively lead to demise of both the fetus and mother. PE remains as a few fatal complications during pregnancy in today's most industrialized countries, and there is no cure for it till date. In most cases, PE leads to premature labor induction which demonstrates the risks for premature neonates (Zabul et al. 2015; Ghosh et al. 2014; Aouache et al. 2018).

At the cellular level, PE is associated with release of free radicals generated by the placenta. Placental-borne free radical stresses are considered as major molecular determinants of maternal disease. Low oxygen tension-induced oxidative stress improves maternal blood flow that leads to normal placentation. At the molecular level, the placenta of PE patients explains imbalanced reactive oxygen species (ROS) generating enzymes and antioxidants. In ex vivo preeclamptic trophoblast, it is observed that ROS-producing enzyme expression and activity are elevated and Wnt/β-catenin signaling pathway is inhibited that promotes trophoblast invasiveness (Many et al. 2000; Zhuang et al. 2015). Oxidative stress also leads to increased transcription of sFLT1(soluble fms-like tyrosine kinase-1),

an antiangiogenic factor (Huang et al. 2013). As compared to women with normal pregnancies, PE patients show impaired placental antioxidation mechanisms as explained by decreased expression of superoxide dismutase and glutathione peroxidase (Vaughan and Walsh 2002). However, treatment with antioxidants such as vitamins E and C did not significantly alter the disease in PE women, suggesting that ROS could be less integral to the pathways of the human syndrome (Poston et al. 2006).

Mitochondrial stress may lead to ROS generation. Zsengellér et al. established the inverse correlation in expression of mitochondrial enzyme cytochrome C oxidase, with expression of sFLT1 in the syncytiotrophoblast cells of preeclamptic placentas (Zsengellér et al. 2016). Based on a study on inhibition of HIF-1α by hydrogen sulfide donors, Covarrubias et al. demonstrated that pretreatment with a mitochondrial-targeting hydrogen sulfide donor AP39 may decrease sFLT1 expression in human syncytiotrophoblasts which brings enhancement in cytochrome C oxidase activity in a dose-dependent manner in both normal and PE placentas, which prevents the release of ROS and subsequent stabilization of HIF-1α (Covarrubias et al. 2019). Several other promising studies have also been reported with mitochondrial antioxidants in animal models of PE (Vaka et al. 2018).

Another possibility of elevated oxidative stress is the endoplasmic reticulum (ER) stress that is caused by ischemia-reperfusion injury. ER stress is observed in the deciduas and placenta of patients with restricted fetal growth and PE that also triggers apoptosis of decidual cells and cytotrophoblast by activating UPR (unfolded protein response). Another leading signaling pathway implicated in PE is a transmembrane kinase PERK (PKR-like endoplasmic reticulum kinase) that downregulated translational burden of ER and upregulates proapoptosis (Lian et al. 2011; Fu et al. 2015). Interestingly, a recent study suggested a synergism between ATF4 (activating transcription factor 4), a transcription factor downstream of PERK, and ATF6, a transcription factor regulator of misfolded proteins in ER homeostasis, which negatively regulate the transcription of *PlGF* (placental growth factor), which is a proangiogenic factor central to the pathogenesis of preeclampsia (Du et al. 2017; Mizuuchi et al. 2016).

12.6.3 Maternal Diabetes

Infants born to diabetic mothers have a higher chance of congenital abnormalities and growth disorders than those born to nondiabetic mothers, according to previous research. The cellular mechanisms that cause diabetes in pregnancies remain unclear. The developmental complications are most likely driven by countless factors, and hence, the etiology is presumably multifactorial (Sadler et al. 1989; Eriksson and Borg 1993; Buchanan et al. 1994). One teratological pathway in embryos exposed to a diabetes-like environment involves increased activity of ROS, impaired antioxidative defense, or both (Eriksson and Borg 1991). An increased production of superoxide inside mitochondria of tissues exposed to high-glucose concentrations has lately been proposed as a common mechanism for all diabetic problems, in keeping with the idea of ROS-mediated embryopathy (Nishikawa et al. 2000; Brownlee 2001). Elevated ROS leakage and impairment of the cytosolic glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase could be a result of excessive ROS synthesis in mitochondria (GAPDH). This enzyme has shown sensitivity toward ROS in a number of oxidative stress scenarios. The thiol group of cysteine residue 149 in active site of the enzyme is responsible for this sensitivity (Rivera-Nieves et al. 1999). Reduced enzyme activity is caused by the oxidation of the thiol group by NO or ROS, which may be associated with the development of embryonic dysmorphogenetic alterations (Morgan et al. 2002).

12.6.4 PCOS

Reproductive aged women are prone to frequent multifactorial endocrine disorders of which PCOS is the common one and considered as the primary reason for anovulatory infertility (Joham

et al. 2015). Chereau in 1844 foremost explained it as the variation in ovarian morphology (Chéreau 1844). In 2003, the European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) established the diagnostic norm for PCOS, based on the detailed research of the last decades, called as the Rotterdam Consensus Criteria. PCOS displays extreme diversities with clinical characteristics like menstrual disorder, secondary amenorrhea, serum hormone abnormality, hairiness, acne, obesity, and infertility (ESHRE and Group 2004). In spite of having an extensive record of research, its specific causal factor still remains unrevealed. At the present time, a pivotal part is played by oxidative stress, not only for PCOS but also for numerous other diseases. It is a known fact that extremely intricate antioxidant enzymatic and nonenzymatic systems manage the generation and distribution of intracellular ROS. However, a thorough knowledge of oxidative stress-induced PCOS mechanisms is required for its prevention and treatment. ROS elevation conducts the discharge of Ca^{2+} ions from endoplasmic reticulum and balance of storage and depletion of intracellular Ca^{2+}. Increased levels of Ca^{2+} impart detrimental effects like imbalance in the mitochondrial membrane and failure of adenosine triphosphate (ATP) synthesis, which cause preliminary necrosis of the cell. According to research, women with PCOS develop follicular arrest because of calcium dysregulation, consequently leading to reproductive and menstrual dysfunction (Mohammadi 2019; Rashidi et al. 2009).

The pathogenesis of insulin resistance in PCOS patient revealed by numerous studies showed that elevated OS leads to various protein kinase activations to trigger serine/threonine phosphorylation of insulin receptor substrate (IRS), which inhibit normal tyrosine phosphorylation of IRS, and directs in degradation of IRS (WANG et al. 1998; Runchel et al. 2011; Brown and Sacks 2009). ROS can activate various pathways including c-Jun *N*-terminal kinases (JNK) which is a component of transcription factor activator protein-1 (AP-1) and p38 pathways. The transcription of various genes like cytokines, growth factors, inflammatory enzymes, matrix metalloproteinase, and immunoglobulins is controlled by activator protein-1 (AP-1). Low-intensity inflammation and increased inflammatory cytokines are related with PCOS, resulting in the pathogenesis of the disease (Diamanti-Kandarakis and Dunaif 2012).

Polyunsaturated fatty acid side chains of the plasma membrane are the site of lipid peroxidation or that of any organelle that contains lipid. Owing to the presence of hydrophobic tail and lipid solubility, vitamin E in these chain reactions can snap and function as antioxidant (Abuja and Albertini 2001; Agarwal et al. 2012). Markers that signify the level of lipid peroxidation like thiobarbituric acid reactive substances, oxidized low-density lipoprotein, and malondialdehyde (MDA) amplify considerably in patients with PCOS in comparison to healthy individuals (González et al. 2006; Nur Torun et al. 2011).

As the oxidation capability of guanine residues is greater than cytosine, thymine, and adenine, DNA oxidation takes place. ROS invasion is highly detrimental to mitochondrial DNA, because of O^{2-} production through electron transport chain (Cooke et al. 2003). DNA damage caused by free radical and failed antioxidant defense has been indicated to be the causative agent for cancer. Dinqer et al. assessed DNA damage caused by increased H_2O_2, which can be used as a marker for DNA detection to oxidation in PCOS women. Ovarian cancer and PCOS connection can be described by considerable spike in DNA damage by H_2O_2 (Dincer et al. 2005).

12.6.5 Hydatidiform Mole

A molar pregnancy (also known as hydatidiform mole) is a form of gestational trophoblastic disease (GTD). Chromosomal anomalies during conception lead to aberrant growth of placental tissues, resulting in this type of pregnancy loss. This condition arises especially when a cluster of fluid-filled cells is developed from a fertilized egg instead of a fetus. Molar pregnancies cannot be sustained till birth and do not result in functional fetus, unless in extremely rare circum-

stances. Although most of the molar pregnancies are not cancerous, the tissue can develop malignancy in certain instances. Molar pregnancies can cause severe clinical complications, demanding months of precautionary supervision following treatment, which generally involves dilation and curettage (D & C), a process that removes conception tissue products from the uterus (Sun et al. 2016).

12.6.6 Ovarian Epithelial Cancer

The fifth major reason of cancer mortality is ovarian cancer, with demise from gynecologic malice being the primary reason and the second most frequently identified gynecologic disease; however, the fundamental pathophysiology remains unclear (Saed et al. 2017; Rojas et al. 2016). Epithelial ovarian cancer is a heterogeneous ailment with reaction to molecular biology, histopathology, and clinical outcome. The top-grade serous ovarian cancer (HGSOC) being the typical and extensively researched progressive levels of tumors for the most part are sourced from epithelial cells. Their origin can be from endometrioid, serous or mucinous cells placed on the surface of the epithelium belonging to the fallopian tube or ovary (Blagden 2015).

Numerous diseases are caused due to the involvement of oxidative stress such as cancer. The initiation, elevation, and advancement of tumor cells are altered as there is modification in the biological redox environment (Reuter et al. 2010). The major cellular processes that manage the stability of cell development and apoptosis are influenced by the constant production of free radicals along with oxidants. It portrays a significant function in the commencement of various cancers. Oxidants initiate and assist the oncogenic phenotype or bring on apoptosis, by considering the level of ROS and RNS in the cellular surroundings, serving as antitumor representatives (Wang and Yi 2008). A number of transcription factors regulate the interpretation of genes important to the growth and development of cancer cells which are known to be managed by oxidative stress. This includes hypoxia-inducible factor (HIF)-1α, nuclear factor (NF)-κB, peroxisome proliferator-activated receptor (PPAR)-γ, activator protein (AP)-1, β-catenin/Wnt, and nuclear factor erythroid 2-related factor 2 (Nrf2) (Reuter et al. 2010).

It is important to note that ROS and RNS produce genetic mutations, altering gene expression along with triggering DNA damage and thus suggesting to be the causative factor of numerous pathologies (Rojas et al. 2016; Reuter et al. 2010; Roos et al. 2016). Flawed DNA owing to ROS and RNS is acknowledged to be a leading factor to develop multiple cancer types (Waris and Ahsan 2006). The DNA bases are revised by oxidative stress by base pair substitutions instead of deletions and insertions of the base. Mutations result whenever there are alterations in GC base pairs; however, AT base pair alteration does not cause the same (Retèl et al. 1993). G to T transversions are the consequences of guanine alterations in cellular DNA that is the most responsible factor to produce ROS and RNS (Waris and Ahsan 2006). The DNA belonging to oncogenes or tumor suppressor genes can establish the commencement of cancer if the modification of G to T in the DNA is not restored. The DNA belonging to oncogenes or tumor suppressor genes can initiate cancer, if the modification of G to T in the DNA is not restored. Thymidine glycol, 5-hydroxymethyl-2′-deoxyuridine, and 8-OHdG are among the few oxidized forms of DNA bases which are recognized sign of DNA impairment caused by free radical (Roos et al. 2016).

Cell migration is amplified by free radicals and oxidants, which leads to increase in tumor invasion and metastasis, resulting in mortality of cancer patients. ROS enables NF-κB to maintain communication of intercellular adhesion protein-1 (ICAM-1), a cell surface protein in numerous cell variants. Owing to trigger in OS, interleukin-8 (IL-8) initiated increased expression of ICAM-1 on neutrophils, amplifying neutrophil movement through the endothelium, which is principal in tumor metastasis (Reuter et al. 2010). Cell migration and resulting tumor invasion are managed by the increase in distinct matrix metalloproteinase (MMPs) enzymes, in the downregulation of vari-

ous factors of the extracellular matrix and basement membrane (Reuter et al. 2010; Westermarck and Kähäri 1999). Free radicals particularly H_2O_2 and NO magnify the function of MMPs, like MMP-2, MMP-3, MMP-9, MMP-10, and MMP-13, due to the enabling of Ras, ERK1/2, p38, and JNK, or the inactivation of phosphatases (Reuter et al. 2010; Westermarck and Kähäri 1999). As a matter of fact, the chief origin of ROS, the NAD(P)H oxidase family of enzymes, is connected to advancement of tumor cells in lung and pancreatic cancers (Rojas et al. 2016; Reuter et al. 2010). Hence, it authenticates ROS to be the major cause in the activation of different cancer types.

12.6.7 Spontaneous Abortion and Recurrent Pregnancy Loss

Recurrent pregnancy loss (RPL) can be termed as the loss of three pregnancies consecutively prior to 20 weeks from the gestational period or fetal weight having less than 500 gms which can affect approximately 30% to 50% of conception before completion of the first trimester. Spontaneous abortion is also a sudden pregnancy loss before 20 weeks of carrying the embryo without intervening any outer factor, and 15–20% of clinical pregnancies are affected from it. RPL can be said as an annoying clinical inconvenience which affects 0.5–3% of fertile group of females from which 50–60% cases are idiopathic. Besides, a primary factor of spontaneous pregnancy loss is due to chromosomal abnormalities, and ROS-generated oxidative stress also might have some probability to participate in fertility dysfunctions like idiopathic recurrent pregnancy loss, spontaneous abortion, defective embryogenesis, hydatidiform mole, and drug-induced teratogenicity. According to research, both systemic and placental oxidative stresses are responsible in the pathophysiologic condition of frequent abortion and RPL. Impaired placental vascularization, oxidant-induced endothelial damage, and immune malfunction are the multiple factors considered for idiopathic recurrent pregnancy loss (Gupta et al. 2007).

As previously stated, there is an oxidative outburst in the placenta between 10 and 12 weeks of pregnancy. After the gush of antioxidant pursuit, the normal level of OS is restored, and the placental cells accustom slowly to the freshly oxidative environment (Jauniaux et al. 2000). In the event of miscarriage, the arrival of maternal intraplacental circulation happens intermittently before time between 8 and 9 weeks of gestation as compared to normal pregnancies (Jauniaux et al. 2000). These placentas show increased concentration of HSP70, nitrotyrosine Hempstock, 2003 #117} (Jauniaux et al. 2003), and markers of apoptosis in the villi, indicating oxidative damage to the trophoblast, thereby terminate the pregnancy (Burton and Jauniaux 2011). During early pregnancy, antioxidant enzymes are not capable to resist the high levels of ROS; rather, a gradual rise in activity occurs with growing gestational age (Jauniaux et al. 2000). If OS happens way too soon in pregnancy, it can damage placental growth and magnify syncytiotrophoblastic degeneration, concluding in the termination of pregnancy (Gupta et al. 2007). Patients with RPL have higher concentrations of plasma lipid peroxides and GSH, as well as lower amounts of vitamin E and β-carotene, which supports the spontaneous abortion process (Şimşek et al. 1998). GSH levels in the plasma of women with a history of RPL were also reported to be significantly higher, reflecting a response to increased ROS (Miller et al. 2000). A different research revealed that patients with idiopathic RPL have extremely reduced levels of the antioxidant enzymes GPx, SOD, and catalase, as well as elevated ROS and MDA levels. Total antioxidant capacity, serum prolidase, and sulfhydryl levels (markers of oxidative stress) have presented significant correlation in women with early pregnancy loss (El-Far et al. 2007).

12.6.8 Intrauterine Growth Restriction (IUGR)

Newborns with birth weight less than tenth percentile are termed as intrauterine growth. 10% of infants are concerned with this state and hence

spike the possibilities of perinatal morbidity and death. Components which majorly cause IUGR include placental, fetal, and maternal factors (Chauhan et al. 2009). A key source of IUGR is preeclampsia which grows in the placenta from uteroplacental inadequacy and ischemic procedures (Scifres and Nelson 2009). Research suggests patients having IUGR progress into OS owing to placental ischemia distress secondary to underdeveloped spiral arteriole. Features of IUGR patients include disproportioned wounds and restoration, along with uncommon progress of the villous tress, making them prone to exhaustion of syncytiotrophoblast, resulting in restricted control of convey and secretory purpose. Hence, in the growth of IUGR, ROS and OS are acknowledged as major components and are produced by potent sources like ischemia and reperfusion trauma (Biri et al. 2007). The controlling apoptotic function of p53 is notably elevated in relation to hypoxic environment in villous trophoblast (Levy et al. 2000); (Levy et al. 2002; Heazell et al. 2008) and signs an increased level of apoptosis secondary to hypoxia reoxygenation than from hypoxia alone. In IUGR placenta, reduction in translation and signaling of proteins sums to overpowering of OS (Yung et al. 2008).

12.6.9 Fetal Death

Fetal death can also be referred to as stillbirth which is described as the unplanned intrauterine death of the fetus occurred at any stage of the pregnancy after 20 weeks of gestation or more. Reports says hypertension, diabetes, multiple gestations, obesity, older maternal age, growth restriction, and preeclampsia like earlier pregnancy complications, history of miscarriage or stillbirth, exposure to alcohol, smoking or any drugs, or any racial group like non-Hispanic black might be some risk factors to induce fetal death. ROS-induced oxidative stress has physiological and pathological function in the placenta, embryo, and fetus. Oxidative stress in the uterus is a consequence of prenatal hypoxia, nutritional deficiency or overnutrition, and excessive glucocorticoid exposure which occurs to the mother (Chen et al. 1999; Morriss 1979; New and Coppola 1970). Among all of these factors, prenatal hypoxia is a condition arises in the early postimplantation phase which is a prerequisite for preliminary organogenesis, and the embryo is utmost reactive to surrounding oxidative stress on account of poorly developed antioxidant defense. As soon as uteroplacental circulation continued, the embryo progresses toward being immune to oxidative stress by amplifying antioxidant defense system (Schafer and Buettner 2001). The measure of oxidative tone and its oscillations is defined as redox switching that modulates the density of the cells in the embryo in the direction of proliferation, apoptosis, differentiation, or necrosis. Altogether, numerous occurrences revealed a major function of ROS in the embryo. Moreover, during embryonic growth, special signaling tracks can be modified by ROS. ROS majorly affects cells and behaves as second messengers by controlling major transcription factors that modulate gene expression in the embryo. Of the numerous transcription factors that are susceptible to redox reactions, nuclear factor jB (NF-kB), hypoxia-inducible factor (HIF-1), redox effector factor-1 (Ref-1), activator protein-1 (AP-1), nuclear factor (NF)-E2 related factor 1 (Nrf-1), and wingless and integration site for mouse mammary tumor virus (Wnt) are important to cell signaling pathways that control proliferation, differentiation, and apoptosis, therefore having a primary function in the embryo's growth (Dennery 2007).

12.7 Conclusion

The delicate balance between ROS generation and cellular antioxidant defense in the elixir of aerobic mode of life and female reproduction is no exclusion. Albeit low levels of ROS are always desirable for maintenance of cellular redox homeostasis and normal physiology, an excess in general leads to pathological states. Both obesity/overnutrition and malnutrition, overexercise, and lifestyle factors such as consumption of alcohol and recreational drugs exert noxious effects of female reproduction. Preeclampsia, gestational

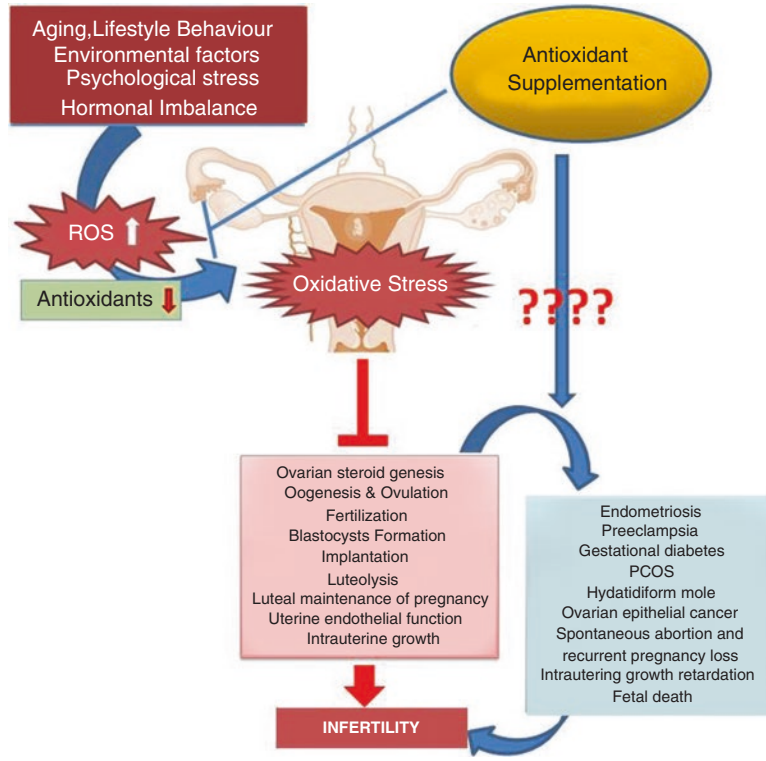

Fig. 12.1 Schematic representation of oxidative stress-induced impairment of female reproduction

diabetes, endometriosis, etc. have oxidative predominance. There are a good number of studies mostly on animals regarding positive impact on female reproduction, while the same on human ailments is controversial (Fig. 12.1). Therefore, future studies may be targeted in understanding the underlying molecular mechanism(s) via high-throughput technologies such as multiomics platforms for personalized medical care.

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