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Balancing Act: Navigating Oxidative Stress in Pregnancy for Optimal Health

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Abstract

Oxidative stress refers to a state of balance involving the generation of reactive oxygen species (ROS) and the body's capacity to counteract their harmful effects. ROS are naturally occurring molecules that, if not adequately regulated, can damage cells and tissues if not properly managed. During pregnancy, ROS levels fluctuate and play a role in various developmental processes. However, an excessive accumulation of reactive oxygen species can lead to oxidative stress, which is linked to numerous complications during pregnancy.

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1. Introduction

Pregnancy presents a metabolic challenge for both the mother and the developing foetus. Even under normal circumstances, it is associated with higher levels of oxidative stress (OS) compared to the non-pregnant state [1, 2]. The placenta is a significant provider of this OS [3, 4] due to its high metabolic rate and increased amount of mitochondrial activity. The presence of an intrauterine operating system (OS) during pregnancy is a natural response to the energy needs of the foetus and placenta [5], as shown in Figure 1 because of the low levels of antioxidant enzymes in placental tissues during the first trimester, trophoblastic cells are more vulnerable to damage caused by oxygen [6]. Furthermore, many studies examine effects of OS on the physiological status of the mother and foetus throughout pregnancy, focusing on the identification of putative biomarkers that play a bigger role in reducing the likelihood of difficulties related to pregnancy and childbirth. A typical pregnancy is a carefully planned sequence of transient, intricate events that includes placentation, parturition, and decidualization [7, 8]. A healthy pregnancy requires certain chronological transitions, and any deviation from this could have an impact on the health of the mother and the foetus [8]. Pregnancy causes a normal systemic inflammatory response that elevates the amount of reactive oxygen species (ROS) in the bloodstream. The placenta, serving as the principal organ responsible for regulating this condition, is the predominant generation of reactive oxygen species (ROS) throughout pregnancy [9]. Damage can occur due to increased oxidative stress during pregnancy [10, 11]. Elevated levels of oxidative stress are mitigated by an upregulation in the production of antioxidants [12]. Oxidative damage may spread to distant organs if oxidative stress exceeds the placenta's antioxidant defenses. This review aims to investigate the influence of free radicals and oxidative stress on both maternal and the growth of foetus through pregnancy. It aims to elucidate the molecular mechanisms of oxidative stress, its clinical ramifications, and possible therapies to alleviate these side effects.

2. Reactive Nitrogen and Oxygen Species

Numerous biological applications result in the production of RNS and ROS. They serve as mediators and regulators, ensuring appropriate cellular functioning when released in physiological proportions [13]. Nitric oxide and proxy nitrite are

examples of RNS [14]. ROS include singlet oxygen, peroxyl radical, hydroxyl radical, hydroperoxyl radical, superoxide radical anion, and hydrogen peroxide [15]. The first effect of ROS generation is the inner cell [16, 17]. The Electron Transport Chain (ETC), consisting of five protein complexes located in the convoluted inner membrane of the mitochondria, serves as the site for these biological processes. A small fraction of electrons may be released during this process and combine with O_2 to form O_2-. Manganese superoxide dismutase (MnSOD) and copper-zinc superoxide dismutase (Cu, Zn, SOD) located in the matrix and intermembrane space of the mitochondria, respectively, transform superoxide that remains within the mitochondria into hydrogen peroxide (H_2O_2). Subsequently, H_2O_2 can undergo reduction to become H_2O, leave the mitochondria, or engage in interactions with mitochondrial proteins. Oxygen is generated, which is one of several processes that occur outside of the mitochondria. Based on the stress-induced premature senescence theory, low levels of various stress-inducing chemicals, like H_2O_2, deplete the ability of actively dividing cells to replicate and result in the buildup of aged cells in inflammatory conditions. The senescent cells may be responsible for activating phagocytic cells and inducing a condition of micro-inflammation. The fatty acids in peroxisomes, which produce H_2O_2, are another illustration of a non-mitochondrial process when it comes to reactivity [18]. They can originate from a variety of sources, either endogenously or exogenously. The electron transport chain is the mitochondrial respiratory chain [19]. Exogenous sources encompass a variety of substances and factors that can contribute to health risks. These include radiation, industrial solvents, pesticides, heavy metals, transition metals, and some drugs such as paracetamol and halothane [20].

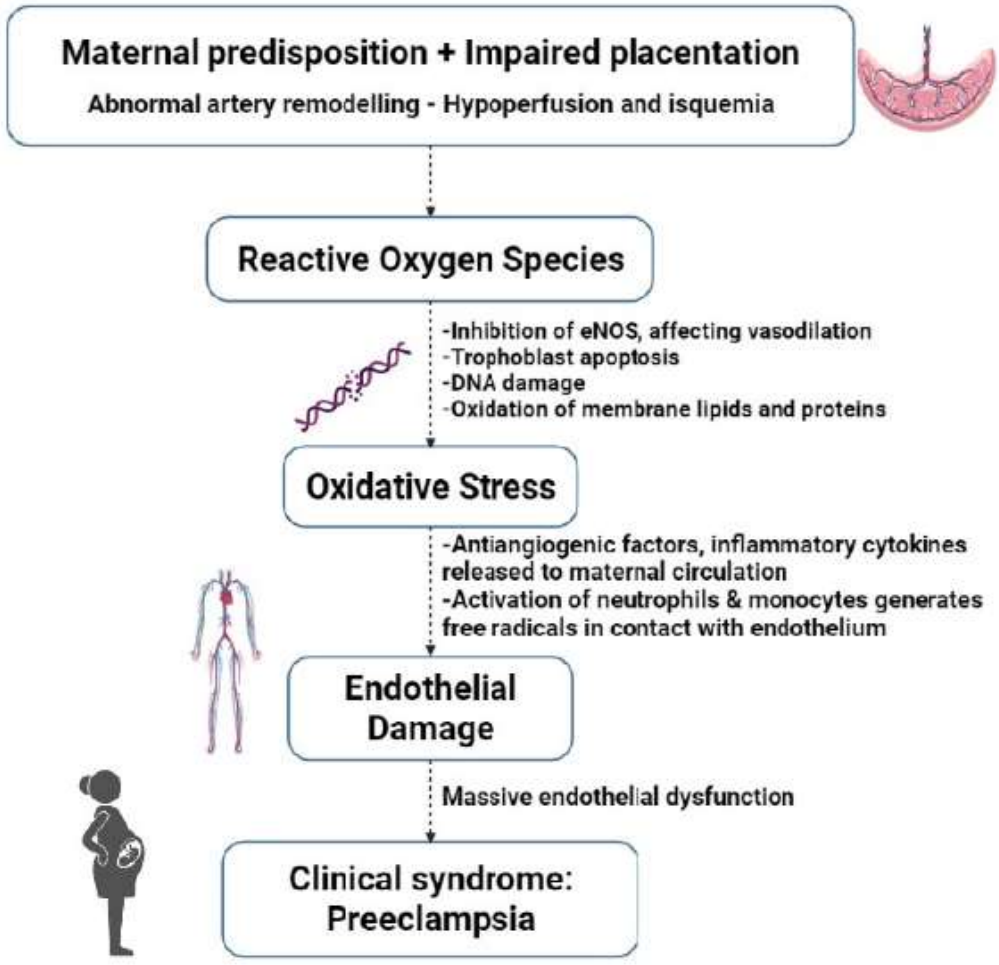

Figure 1: Oxidative stress during pregnancy.

3. Oxidative stress

Reactive oxygen species (ROS) are compounds that possess a minimum of one oxygen atom and can produce free radicals. They engage in cell signaling processes, which are vital to cell activity at the level of biology [21]. On the other hand, an overabundance of ROS can harm lipids, proteins, and DNA within the cell [22]. Antioxidants reduce cell death and maintain the integrity of cellular membranes by protecting cells from peroxidation processes. An imbalance of antioxidant capability is referred to as "oxidative stress" and is significant in the development of several diseases, such as cancer [23], neurological [24], and cardiovascular conditions [25]. Numerous reproductive and pregnancy diseases, including subfertility, miscarriages, maternal vascular disease, and preterm labor, have been linked to oxidative stress. Glutathione peroxidase and superoxide dismutase are examples of antioxidant enzymes that require iron, zinc, and selenium as co-factors. Antioxidant therapy can treat or prevent disease. Antioxidants that are frequently utilized in therapy include flavonoids, selenium, and folic acid, with different vitamins. Monoamine oxidase activity continuously produces H_2O_2, and normal mitochondrial respiration releases O_2 [26, 27]. Reactive forms of iron or copper release free radicals [27]. Free radicals are substances, along with other compounds, that have one or more unpaired electrons regardless of their source, such as radiation [28, 29]. Nevertheless, H_2O_2 can traverse the mitochondrial and plasma membranes and access DNA. Upon arrival, tightly bound transition metals produce hydroxyl radicals (OH) in the nearby vicinity, leading to DNA damage. An elevated level of oxidized bases, specifically 8-hydroxy-deoxyguanosine, serves as a notable indicator of DNA damage caused by the Fenton reaction, which is facilitated by iron or copper. Various tests can be utilized to identify DNA breaks, including both single and double-strand breaks [30]. Protein carbonyls are formed when free radicals react with specific amino acid residues, such as arginine, histidine, lysine, and proline, causing oxidation of sulfhydryl groups and hydroxylation of tyrosine and phenylalanine. Additionally, certain compounds can serve as indicators of free radical harm [31].

4. Oxidants

Reactive oxygen species (ROS) and Reactive Nitrogen Species (RNS) consist of diverse reactive compounds. These molecules can oxidize substrates under specific conditions, as indicated in Table 1.

Table 1: List of the reactive oxygen/nitrogen species with chemical formula.

Reactive Oxygen Species	Chemical Formula
Superoxide radical	$O_2^{\bullet-}$
Hydroxyl radical	$^{\bullet}OH$
Singlet oxygen	O_2
Hydrogen peroxide	H_2O_2
Peroxyl radical	$ROO^{\bullet}$
Alkoxyl radical	$RO^{\bullet}$
Peroxynitrite	$ONOO^-$
Hypochlorous acid	HOCl
Peroxynitrous acid	ONOOH
Nitric oxide	$^{\bullet}NO$
Nitrogen dioxide	$^{\bullet}NO2$
Ozone	O3

5. Antioxidants

Antioxidants are chemical substances that impede or diminish [32]; in comparison to the substances that can undergo oxidation, they are present in modest quantities, effectively slowing down or preventing the oxidation of those substances. Subsequently, the term was revised to encompass compounds that repair oxidative damage to the system, in addition to substances that delay, prevent, or remove such damage to a target molecule [33]. Effective antioxidants possess the capacity to postpone the process of oxidation or impede the formation of harmful free radicals. They can also disrupt the chain reaction of autoxidation that produces free radicals and oxidants. Furthermore, they serve as agents that decrease the oxidation state of substances and bind to metal ions, so converting hydroperoxides into more stable

molecules [34, 35]. There are additional methods involve the sequestration and confinement of metallic ions that facilitate oxidation, such as iron and copper, by the utilization of specialized proteins that exhibit affinity towards these metals [36]. Transferrin, metallothionein, haptoglobin, and ceruloplasmin are all examples of such proteins. Food antioxidants help prevent oxidative processes that might cause a decrease in their overall quality. The health benefits of antioxidants are dictated by its systemic bioavailability, which refers to how widely the material can be dispersed throughout the body. Moreover, the precise concentration of the antioxidant that reaches certain organ regions is of utmost importance, as well as its ability to perform its intended function effectively. Multiple studies have demonstrated that the consumption of antioxidants, particularly in large quantities, might result in toxicity due to their prooxidative properties [26-28].

6. Role of Free Radicals and Oxidative Stress in Pregnancy and Their Effects on the Foetus

Free radicals, extremely reactive particles characterized by unpaired electrons, significantly influence human health and disease. Although they are crucial for common cell functions, including transmission and infection safety, the asymmetry between their syntheses may result in oxidative stress, a condition marked as a high level of ROS that surpasses the human body's protective antioxidants [37]. The presence of oxidative stress while pregnant significantly affects both mother and foetal health, with serious consequences for the baby's development [38, 39]. Pregnancy induces biochemical and physiological modifications to facilitate the development of the foetus. These alterations elevate oxygen consumption and metabolic activity, leading to an augmented generation of free radicals, especially ROS. Free radicals, including O_2^-, OH^-, and H_2O_2, are predominantly produced by the mitochondrial respiratory chain and enzymatic systems, as shown in Figure 2. The human body's immune system, comprising enzyme-based systems that include SOD, catalase, and glutathione peroxidase (GPx), together with non-enzymatic antioxidants, including vitamins C and E, are essential for neutralization-free radicals and reducing oxidative stress [38-40].

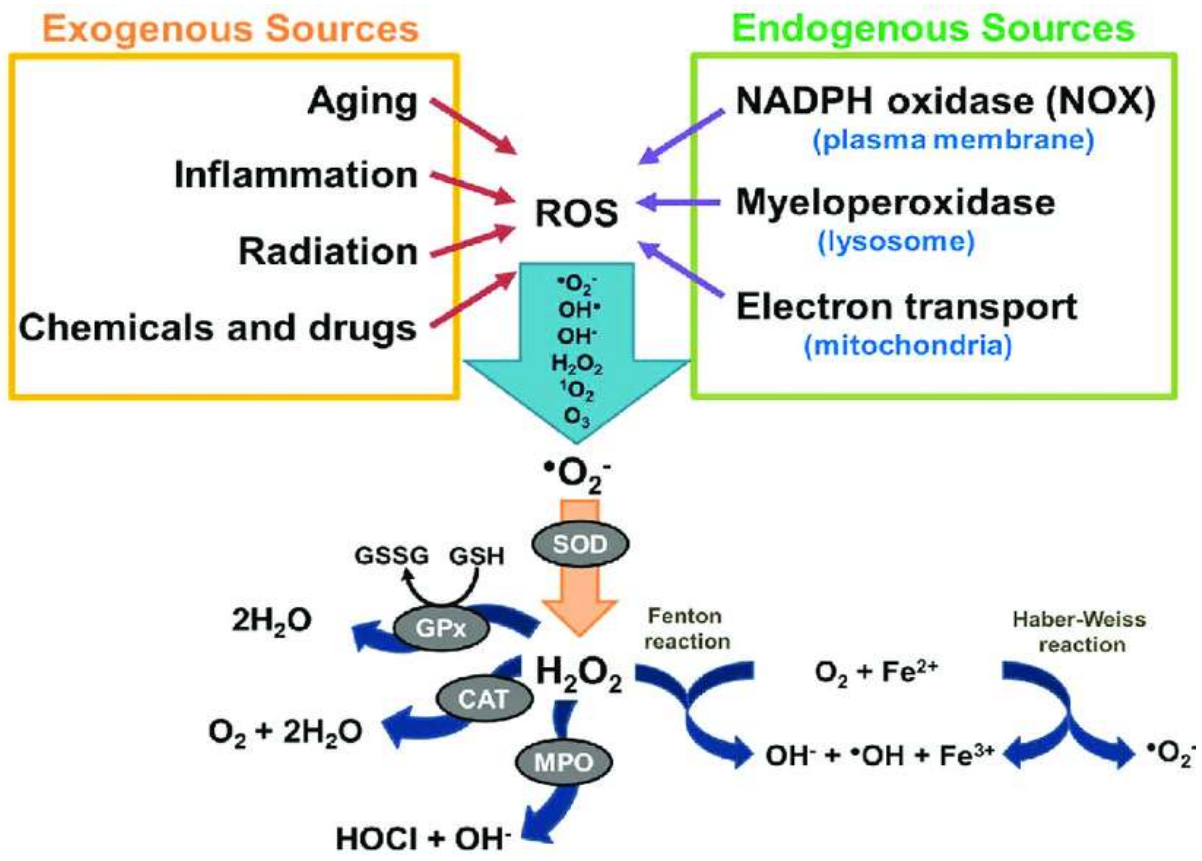

Figure 2: Sources of ROS and key ROS molecules in signaling.

7. Pregnancy Related with Oxidative Stress

In a typical pregnancy, the development of foetal tissues and organs necessitates a sufficient supply of nutrients and oxygen, collectively with their reaction form created in the maternal body, which affects replication, differentiation, and the maturity of the growing cells. Their equilibrium activity and sustaining the equilibrium of oxidative Processes are essential components for optimal development and body operation [41]. Numerous research investigations demonstrate that oxidative stress, characterized by the excessive and unregulated formation of reactive oxygen compounds (ROS), adversely affects pregnancy, the mother's well-being, and foetal development. It is responsible for improper embryo implantation, miscarriages, early births, low birth weight, and congenital abnormalities. It also diminishes maternal immune function and respiratory adaption of neonates immediately post-delivery. The primary cause of these illnesses is the inadequate delivery of nutrients and oxygen to the baby, primarily due to hypoplasia and abnormalities which is placenta's function [41-43]. Study comparisons of pregnant and non-pregnant women, show that total plasma antioxidants (TAS) significantly decrease during the first trimester of pregnancy. During both the second and third trimesters of gestation, total plasma antioxidant capacity (TAC) rises, reaching its zenith in the final week of pregnancy at levels comparable to those previously recorded, in women who are not pregnant [44]. Research conducted by other scientists suggests that diminished TAS readings during pregnancy are attributable to decreased serum bilirubin, vitamin E and albumin concentrations [45]. Other research suggests that plasma superoxide dismutase activity diminishes in a normally progressing pregnancy [46]. Pregnancy physically elevates the concentrations of total cholesterol, triglycerides, and LDL (low-density lipoprotein) cholesterol in plasma, that agree with Giuseppe Lippi, (2007) also, his study demonstrated that all lipid markers assessed were considerably altered by gestational age, commencing from the second stage. Specifically, women in the second and third trimesters had elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), TC/HDL ratio, and lipoprotein levels [47]. Indicators of oxidative stress correlate with an elevation in lipid peroxides following 25 weeks of gestation. Thus, the natural biomarker for oxidative stress and the degree of lipid peroxidation is the increased concentration of malondialdehyde in the plasma of pregnant women this concurs with Rosy Lekharu (2014) [48]. Several studies have indicated a positive correlation between a consumption of nutrient / dense diet and elevated anti-oxidant level [45-49]. Oxidative stress, mostly caused by excessive formation of oxygen degradation products in mitochondria, adversely affects freshly proliferating cells. It undermines their integrity perhaps already at an initial phase of embryogenesis. Factors influencing the formation of elevated amounts of reactive oxygen species and the associated diseases may include chronic stress, environmental pollution, teratogenic agents and insufficient physical activity. Impact of pharmaceuticals and toxins, or inadequate diet. It induces structural anomalies in DNA that may result in pre-eclampsia, early miscarriages, foetal abnormalities, foetal growth limitation and congenital malformations [50-52]. Researchers identified increased concentrations of oxidative stress indicators in the blood serum of pregnant women during the initial prenatal screening at 11-14 weeks of gestation showed a high level (<1:300 as per the Foetal Medicine Foundation) risk of prenatal anomalies. Subsequently, following extensive investigation and meticulous analysis, they validated the substantial disparity in oxidative stress levels amongst patients with health conditions, sick foetuses complicated by chromosomal abnormalities as well as other abnormalities [53]. The disruption of DNA structure due to an imbalance between antioxidant and oxidant levels in the body has intensified attention on the role of reactive oxygen species (ROS) in the cause of illness, pertaining to genetic anomalies. Oxidative stress that compromises the integrity of a deoxyribonucleic acid molecule results in chromosomal abnormalities. Pagano and Castello demonstrated distinctive modifications in vivo of mitochondrial functionality, resulting in elevated ROS levels in the cell as a distinctive alteration about trisomy 21 [54]. Examinations of diverse oxidative stress indicators in maternal blood, foetal tissues and amniotic fluid demonstrated a distinct association with Down syndrome. Notable alterations significantly contributed to the impairment of numerous tissue enzymes. It can be inferred that they contributed to the aetiology of this anomaly [54, 55].

8. Marker of oxidative stress

Oxidative stress markers are molecules or compounds that indicate the presence of oxidative damage in the body. These markers can be measured in various biological samples, such as blood, urine, or tissue, to assess the level of oxidative stress and its potential impact on health.

Lipid peroxidation markers: These markers indicate damage to lipids, which are essential components of cell membranes. Common lipid peroxidation markers include: Malondialdehyde (MDA) 4-Hydroxynonenal (4-HNE) and Isoprostanes. MDA a by-product formed during the oxidation of lipids, has been utilized as a biomarker to quantify oxidative stress in different biological specimens such as blood, urine, and exhaled breath condensate (EBC) in patients with a variety of conditions, including neurodegenerative disorders, cardiovascular and pulmonary cancer [56,57]. The levels of the lipid peroxidation indicators MDA can be detected in both pregnant women and non-pregnant women [58, 59]. Furthermore, it is worth noting that the levels of MDA are elevated during the initial three months of pregnancy and are much higher compared to non-pregnant women. Additionally, MDA levels continue to rise throughout the course of pregnancy. The Ishihara conducted a study on the levels of lipid peroxides in non-pregnant women and women in different stages of pregnancy (I, II, and III trimesters). The study showed an important rise in the levels of lipid peroxidation products in pregnancy throughout both the third and second-trimester stages compared in women who were not pregnant [58-60]. Protein oxidation markers: These markers indicate damage to proteins, which can affect their structure and function. Common protein oxidation markers include Protein carbonyls, advanced oxidation protein products (AOPP), and Nitro tyrosine. Protein carbonylation is a form of protein oxidation that reactive oxygen species can facilitate. Typically, it pertains to a procedure that generates highly reactive ketones or aldehydes, which can then undergo a reaction with 2, 4-dinitrophenylhydrazine (DNPH) to produce hydrazones. [61, 62]. The breakdown of polyunsaturated fatty acids through oxidation triggers a series of events that result in the creation of several carbonyl compounds, ranging from three to nine carbon atoms in length. Elevated protein carbonyl levels have been seen in the maternal plasma of pregnant women compared to nonpregnant women [63]. Also, the study of Petra L.M. show the levels of protein carbonyls were significantly higher in pregnant women when compared to non-pregnant women ($P < 0.001$) [64]. DNA oxidation markers: These markers indicate damage to DNA, which can lead to mutations and increased risk of cancer. Common DNA oxidation markers include 8-Hydroxy-2'-deoxyguanosine (8-OHdG) and 8-Oxoguanine (8-oxoG). The hydroxyl radical (OH•) is the primary oxygen-free radical responsible for damaging crucial macromolecules, including protein molecules, membrane lipids, and DNA. Many mechanisms, such as the Fenton reaction, can produce the hydroxyl radical. This reaction involves the interaction between hydrogen peroxide (which can penetrate the nucleus) and metals. Furthermore, specific reactive oxygen species (ROS), which can occur naturally or be externally introduced, possess the capability to produce the hydroxyl radical [65]. OH• reacts with DNA bases, especially guanine, to make C8-hydroxyguanine (8-OHGua) or deoxyguanosine (8-hydroxy-2'-deoxyguanosine), which are both nucleosides. Kinga Toboła (2020) and his study show increases levels of (8-OHdG) in pregnancy [66]. Antioxidant markers: These markers indicate the body's antioxidant capacity, which helps to protect against oxidative damage. Common antioxidant markers include: Superoxide dismutase (SOD), Catalase (CAT), Glutathione system Glutathione peroxidase (GPx), and Glutathione reductase and vitamins (Vitamin C and Vitamin E) [66, 67]. Glutathione, Glutathione reductase & Glutathione Peroxidase. Glutathione (GSH) is a tripeptide, scientifically referred to as L-γ-glutamyl-L-cysteinyl glycine, that serves several roles in cells and organisms [67– 70]. It functions as an antioxidant by directly interacting with reactive oxygen and nitrogen species (ROS and RNS) and electrophiles or by serving as a cofactor for different enzymes [71-74]. Glutathione is present in two different states: reduced (GSH) and oxidized (GSSG). Antioxidants and the concentration of glutathione play a vital role in preserving a healthy pregnancy. Glutathione is essential for the growth of the foetus and the formation of the placenta [75]. Glutathione exerts regulatory control on cell differentiation, proliferation, and apoptosis, which are crucial processes in embryonic development. Additionally, it plays a key role in the formation of organs (organogenesis) and the development of the embryo (embryogenesis). The concentration of antioxidants progressively diminishes as pregnancy advances from the initial to the final trimester [73, 76]. The review highlights the various roles that oxidative stressors play during pregnancy, wherein how biological processes including pregnancy and placenta development depend on controlled ROS concentrations. Excessive ROS cause oxidative stress, which leads to issues like pre-eclampsia and pregnancy related diabetes. This could result in the newborn having a higher chance of developing chronic illnesses and a lack of oxygen mutations in the deoxyribonucleic acid. In order to reduce oxidative stress, the study emphasizes the use of

protective antioxidants, which include both dietary and pharmacological approaches.

9. Conclusions

Free radicals (FR), which are often synthesized within living organisms, are highly reactive compounds that possess one or more unpaired electrons. If they are overproduced, they serve as crucial agents in inducing or hastening cell and tissue damage, leading to senescence processes. Pregnancies, especially difficult ones, are characterized by a heightened susceptibility to FR exposure. Moreover, we highlight the significant association between the oxidative status of the typical mother and the neonate, demonstrating that a heightened maternal oxidative stress level correlates to even greater oxidative stress in the newborn, leading to accelerated cellular senescence. The vulnerability of the perinatal period to oxidative stress (OS) suggests that the preventive administration of antioxidants may be beneficial in mitigating or maybe preventing OS-related conditions during pregnancy and in infants.

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