Review

Oxidative Stress in Pregnancy

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Abstract: Recent years have seen an increased interest in the role of oxidative stress (OS) in pregnancy. Pregnancy inherently heightens susceptibility to OS, a condition fueled by a systemic inflammatory response which culminates in an elevated presence of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the circulatory system. The amplified OS in pregnancy can trigger a series of detrimental outcomes such as underdevelopment, abnormal placental function, and a host of pregnancy complications, including pre-eclampsia, embryonic resorption, recurrent pregnancy loss, fetal developmental anomalies, intrauterine growth restriction, and in extreme instances, fetal death. The body's response to mitigate the uncontrolled increase in RNS/ROS levels involves trace elements that take part in non-enzymatic and enzymatic defense mechanisms, namely, copper (Cu), zinc (Zn), manganese (Mn), iron (Fe), and selenium (Se). Determination of ROS concentrations poses a challenge due to their short lifespan, prompting the use of marker proteins, including malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), lipid peroxidation (LPO), catalase (CAT), and glutathione (GSH). These markers, indicative of redox stress intensity, can offer indirect assessments of pregnancy complications. Given the limitations in conducting experimental studies on pregnant women, animal models serve as valuable substitutes for in-depth research. This review delves into the mechanism of OS in pregnancy and underscores the pivotal role of markers in its evaluation.

Keywords: Oxidative stress; pregnancy; trace elements

1. Introduction

Over the last five years, the scientific community has observed a significant surge in investigations probing the role of oxidative stress (OS) in the initiation and progression of many diseases (Pubmed keyword: 'Oxidative stress', yielding 118,239 results 06.10.2023). A substantial number of them is devoted to unravelling the implications of reactive oxygen species (ROS) on the trajectory of pregnancy and its impacts on fetuses and neonates (Pubmed keyword: Oxidative stress AND Pregnancy, yielding 3,117 results 06.10.2023). Nonetheless, the intricate mechanisms responsible for the onset of pathophysiological alterations in response to ROS remain largely elusive. The aim of this paper is to elucidate the importance of reactive oxygen species (ROS) and reactive nitrogen species (RNS), as well as their modulatory effects on pregnancy. Additionally, we scrutinize the repercussions of OS on the maternal and fetal physiological state during pregnancy, with an emphasis on identifying potential biomarkers that could be instrumental in mitigating the risk of complications associated with pregnancy and childbirth. Our analysis is based on the analysis of

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scientific articles sourced from reputable databases such as PubMed, Embase, and the Web of Science. This review encompasses comprehensive review and original research articles, publications in the English language, and articles published in peer-reviewed journals. We excluded brief communications, case reports, and grey literature (e.g., conference proceedings, abstracts). No restrictions were imposed on the publication date. Upon the application of these criteria, a total of 172 papers were shortlisted for review.

2. Free radicals

Reactive nitrogen species (RNS) and reactive oxygen species (ROS) are generated during various biological processes. When released in physiological quantities, they function as mediators and regulators, ensuring proper cellular functioning [1]. RNS include nitric oxide (NO·) and peroxynitrite ($ONOO^-$) [2]. ROS comprise superoxide radical anion ($\cdot O_2^-$), hydrogen peroxide (H_2O_2), hydroxyl radical (·OH), hydroperoxyl radical (HOO·), singlet oxygen ($(1)O_2$), and peroxyl radical (ROO·) [3]. The primary ROS generated during oxygen metabolism is superoxide, which is highly reactive and cytotoxic. Under the influence of superoxide dismutase (SOD), it catalyzes the disproportionation to dioxygen and a significantly less reactive product – H_2O_2, thereby safeguarding cells from toxic oxygen respiration products [4].

The one-electron reduction of O_2 to $\cdot O_2^-$ and its dismutation to H_2O_2 occurs during mitochondrial respiration. H_2O_2 is produced in mitochondria (superoxide dismutase reaction) and peroxisomes (acyl-CoA oxidase reaction). Mitochondria are also involved in generating NO via nitric oxide synthase (NOS). $\cdot O_2^-$ and NO react to form peroxynitrite ($ONOO^-$), a potential source of ·OH [5], which forms in the presence of metals, including copper (Cu) and iron (Fe), and H_2O_2 (Fenton reaction). The non-enzymatic Fenton reaction is the degradation of H_2O_2 catalyzed by Fe^{2+}, resulting in ·OH, and occurs in the endoplasmic reticulum [6].

Other non-mitochondrial reactions include the respiratory burst of phagocytic cells, which are sources of $\cdot O_2^-$. In inflammatory states, according to the stress-induced premature senescence (SIPS) theory, sublethal doses of various stressogenic agents, including H_2O_2, exhaust the replicative potential of proliferating cells and accumulate aging cells, which may be responsible for creating a micro-inflammatory state and activating phagocytic cells. Another example of a non-mitochondrial reaction is the reaction occurring in peroxisomes with β-oxidation of fatty acids generating H_2O_2 [7]. ROS are oxygen compounds exhibiting higher reactivity than molecular oxygen in the ground (triplet) state. They can be generated endogenously or exogenously from numerous sources. The endogenous ones include the mitochondrial respiratory chain, the electron transport chain, the microsomal electron transport chain, oxidant enzymes (xanthine oxidase, cyclo-oxygenase), phagocytes, and cellular auto-oxidation of Fe^{2+} and epinephrine [8,9]. Exogenous sources include alcohol, tobacco smoke, poor diet, intense physical exertion, low temperatures, stress, injuries, heavy metals, transition metals, industrial solvents, pesticides, benzopyrene, radiation, certain drugs like halothane, paracetamol, and bacterial and viral infections [9].

Under physiological conditions, the production of ROS is tightly regulated by the body through the actions of enzymatic and non-enzymatic defensive mechanisms. However, the impact of ROS on cells largely depends on their concentration and duration of action. A brief increase in ROS production is usually well-tolerated by cells and typically results in an enhanced defensive response. However, an intense or prolonged state of OS, triggered by pathogenic factors or harmful external factors, induces damage to cellular components [10].

ROS participate in numerous processes, including muscle contraction, hormone secretion, immune system function, and vascular tension regulation. ROS influence cell growth and differentiation, growth factor activation, mitogenic response, extracellular matrix production modulation, and cell apoptosis. Moreover, reactive oxygen forms cause NO inactivation, pro-inflammatory gene stimulation, and activation of numerous kinases [11].

ROS play a critical regulatory role through various signaling transduction pathways in folliculogenesis, corpus luteum oocyte maturation, and feto-placental development [12,13]. During pregnancy, ROS are naturally produced during implantation, proliferation, differentiation, and

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trophoblastic invasion processes [14]. Their increased production is associated with placental function, among other things [15]. In the first trimester of pregnancy, the oxygen concentration in the placenta is low as it is not yet connected to the mother's circulation, which leads to the generation of ROS that stimulate cell proliferation and angiogenesis, including the production of hypoxia-inducible factors (HIF), vascular endothelial growth factor (VEGF), and placental growth factor (PGF) [15–17]. In addition, nitric oxide (NO) contributes to maintaining vascular tension to increase blood flow in the uterus [18].

3. Oxidative stress

Oxidative stress (OS) is caused by an imbalance between the production and accumulation of free radicals and the capacity of a biological system to detoxify these reactive products [17,19]. It is caused by increased levels of ROS and/or reactive nitrogen species (RNS), or a decrease in antioxidant defense mechanisms, which can lead to chronic inflammation [20–22]. Generated ROS, including $\cdot O_2^-$, H_2O_2, and ·OH, cause damage to proteins, DNA, and lipid peroxidation, which can result in the disturbance of membrane integrity, changes in DNA structure leading to mutations or cytotoxic effects, and cellular metabolism [23]. OS can be a direct or indirect cause of several disease conditions such as diabetes mellitus, neurodegenerative disorders (Parkinson's disease, Alzheimer's disease, and multiple sclerosis), cardiovascular diseases (atherosclerosis and hypertension), respiratory diseases (asthma), cataract development, rheumatoid arthritis, and in various cancers (colorectal, prostate, breast, lung, and bladder cancers) [9,24,25].

Free radicals affect various reproductive processes. For example, gametes are extremely sensitive to damage by ROS and need to be protected to maintain the survival of the species. OS can affect sperm structure and function, including decreased sperm viability, motility, number, and fertilization potential, which can lead to infertility [26,27].

OS is also considered to be responsible for the initiation or development of pathological processes affecting female reproductive processes [27,28]. In the follicular fluid, ROS play an important role in the modulation of oocyte maturation, folliculogenesis, ovarian steroidogenesis, luteolysis, and ovulation [29]. OS can lead to the occurrence of endometriosis, polycystic ovary syndrome, premature ovarian failure, and unexplained infertility [15,30,31]. Furthermore, it has been linked to the adverse effect of repeated ovarian stimulation on reproductive capabilities [32], as well as to the developmental potential of oocytes under *in vitro* conditions [33] or in response to aging [34,35].

Pregnancy is a period of physiological and physical disturbance (adaptation to maintaining the growing fetus and preparation for childbirth and breastfeeding) in order to maintain the proper homeostasis of the mother's body [36]. It is characterized by many physiological changes, resulting in increased basal oxygen consumption and changes in energy substrate usage by various organs, including the fetoplacental unit [37]. Pregnancy is also associated with increased susceptibility to OS generated by the systemic inflammatory response [38,39] and playing a significant role during pregnancy, normal childbirth, and the initiation of preterm birth [40–43]. The systemic inflammatory response in pregnancy leads to the activation of peripheral granulocytes, monocytes, and lymphocytes during the third trimester, which produce large amounts of ROS [44,45]. Common disorders during pregnancy, such as lipid peroxidation and endothelial cell dysfunction, are likely caused by ROS, which attack cell membrane phospholipids and react with polyunsaturated fatty acids, creating lipid peroxides and causing cell damage [46].

The main source of ROS during pregnancy is the placenta [44], which, from early pregnancy, affects the mother's homeostasis. Initially, the placenta has a hypoxic environment [47]. The mitochondria-rich placental activity and high maternal metabolism result in the production of a high level of ROS, mainly $\cdot O_2^-$ and NO, which are important for placental blood perfusion and fetal nutrition [48,49].

By the end of the first trimester, the placenta is fully developed, and there is a threefold increase in oxygen concentration, leading to an increase in ROS levels, primarily in the syncytiotrophoblast. This process is fully regulated by the production of hypoxia-inducible factor 1 (HIF-1α) and the

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expression of genes encoding antioxidant enzymes, including heme oxygenase 1 and 2 (HO-1 and HO-2), copper-zinc superoxide dismutase (Cu/Zn-SOD), catalase, and glutathione peroxidase (GPx) [15–17]. Under physiological conditions, this is under strict control of the body, due to the action of enzymatic and non-enzymatic defense mechanisms [50].

When OS exceeds the antioxidant defense of the placenta, oxidative damage can spread to distal tissues and can lead to many complications and abnormalities during pregnancy [15–17]. Accumulation of ROS leads to underdevelopment and abnormal placental function, which in turn causes disorders in the supply of oxygen and nutrients to the fetus [51,52]. This can cause the adhesion of leukocytes and platelets to the endothelium, as well as the release of cytokines and antiangiogenic factors. In inflammation, generalized vasoconstriction and increased resistance in the placental circulation may be due to a reduction in uteroplacental blood flow and placental dysfunction [53].

OS disrupts placental function and can alter fetal growth through various pathways, including modulation of key nutrient transporters such as Slc2a1 or Slc38a1 and cell death [54–56]. It can cause complications during pregnancy such as embryonic resorption, recurrent pregnancy loss, intrauterine growth restriction, and fetal death [57,58].

OS and inflammatory responses are more pronounced in pre-eclampsia [59], which can lead to low birth weight and fetal developmental abnormalities [60]. Mothers in vaginal delivery and their newborns experience a higher OS than those who undergo elective cesarean section for delivery [61]. During pregnancy, OS is closely associated with nausea and vomiting, and through changes in lipid metabolism it indirectly affects gestational diabetes and fetal macrosomia. It also intensifies tissue damage associated with diabetes. Through pre-eclampsia and pregnancy hypertension, OS increases the risk of premature delivery and maternal mortality [62]. Pre-eclampsia and the associated OS can damage placental DNA, which is probably associated with the disruption of its function and inhibition of fetal growth.

The perinatal period is important for maintaining a balance between the production of free radicals and the functional incompetence of the fetal and neonatal antioxidant system. The values of OS indicators just after birth are elevated in both the mother and the child, and in the following few days in the newborn they continue to rise. It has been shown that mother's milk contains a proportional amount of antioxidants to the child's deficiency, which may indicate its protective role in reducing OS [63].

The impact of the mode of delivery on the level of OS is still being researched. Fogel et al. [64] compared the level of OS in newborns who were born vaginally and through cesarean section. The study, examining the susceptibility of umbilical blood lipids to copper-induced peroxidation, showed an elevated level of OS regardless of the mode of delivery. Vakilian et al. [65], comparing both modes of delivery using thiobarbituric reactive substances (TBARS) as markers of lipid peroxidation, total antioxidant power (TAP), and total thiol molecules (TTM) in the blood of mothers and their newborns, showed that natural childbirth causes an increase in OS compared to cesarean section. Sgorbini et al. [66] showed the same relationship when studying reactive oxygen metabolites (d-ROMs) and biological antioxidant potential (BAP), noting the effective antioxidant defense of newborns, who often coped with ROS better than their mothers.

However, the opposite relationship was shown by Mutlu et al. [67], analyzing OS using antioxidant capacity (TAC), total oxidant status (TOS), OS index (OSI), and lipid hydroperoxide (LOOH) level, Şimşek et al. [68], studying total antioxidative status (TAS), total oxidative status (TOS), oxidative stress index (OSI), malonyldialdehyde (MDA), and glutathione peroxidase (GSH-Px) levels, and Watanabe et al. [69], analyzing derivatives of reactive oxygen metabolites (d-ROMs). They noticed that natural childbirth was associated with decreased OS compared to cesarean section.

Saphier et al. [70], based on the studies of other authors, also did not find significant differences in the level of OS between uncomplicated natural birth and planned cesarean section. More over Hung et al. [71] who found that childbirth is associated with increased placental OS and affects maternal OS, and natural childbirth shows different OS indicators compared to cesarean section.

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An elevated level of OS has been found in patients with gestational diabetes mellitus [47,72,73]. Increased OS load may be responsible for the increased risk of pre-eclampsia and fetal developmental defects [74]. Pre-eclampsia and pregnancy hypertension are major causes of maternal mortality and morbidity and are often the cause of premature childbirth.

OS is further amplified by smoking [75], which has been proven in many studies showing that tobacco smoke carries over 1000 free radicals and enhances both basic and induced lipid peroxidation [76–78]. This also applies to e-cigarettes, which adversely affect the endothelial network by inhibiting the promotion of OS and the adhesion of immune cells [79].

It has been found that prenatal OS may be accompanied by low birth weight of the newborn [80]. Newborns undergo a number of physiological changes that significantly increase both the production of ROS and the possibility of OS occurrence [81,82]. Healthy infants are able to adapt to these changes, but premature and sick newborns are more susceptible to the negative impact of OS due to their immature endogenous and insufficient exogenous antioxidant protection [83,84]. An increasing effect of OS in preterm infants was observed if perinatal conditions (e.g., pre-eclampsia, hypoxia and respiratory failure) or treatment (e.g., oxygen therapy) were present, which reduced their antioxidant capacity and additionally increased ROS production [85,86]. ROS play a role in the pathogenesis of many newborn diseases, such as retinopathy of prematurity, brain hypoxia and ischemia, intraventricular hemorrhage, and chronic lung disease [85,87].

4. Antioxidant system

Free radicals are neutralized by the antioxidant defense system. They are present in small concentrations and significantly prevent the oxidation of substrates [88,89]. Enzymatic and non-enzymatic antioxidants have been distinguished based on their activity in intracellular and extracellular compartments. Enzymatic antioxidants include superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), glutathione transferase, and glutathione reductase (GSR), which can cause the reduction of H_2O_2 to water and alcohol [90].

In mammals, SOD consists of three isoforms: the cytoplasmic Cu/ZnSOD (SOD1), the mitochondrial MnSOD (SOD2), and the extracellular Cu/ZnSOD (SOD3) [91]. Gpx reduces H_2O_2 and lipid peroxides to water and fatty alcohols, then oxidizes glutathione (GSH) to glutathione disulfide (GSSG). CAT catalyzes the conversion of H_2O_2 to water and molecular oxygen, thus protecting cells from the harmful effects of H_2O_2 produced in the cell. This enzyme is most effective during increased OS, when GSH or GPx levels are reduced. Reduced glutathione plays a major role in regulating the intracellular redox state of cells, as it is the main source of reduction equivalents. Thioredoxin reductase is responsible for thiol-dependent reduction processes in the cell. Glutathione S-transferase and H_2O_2 can form spontaneously or through SOD-catalyzed dismutation of $\bullet O_2^-$: $2\bullet O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$. Sulfur carriers are sensors in redox signaling pathways that control and integrate metabolic pathways. The three main redox controls responsible for regulating these carriers are thioredoxins, GSH/GSSG, and the redox couple cysteine/cystine (Cys/Cyss) [92].

Non-enzymatic antioxidants, including vitamin C, vitamin E, glutathione, ubiquinone, flavonoids, and antioxidant cofactors such as selenium, zinc, and copper are capable of removing, capturing, or inhibiting the formation of ROS [89]. These substances inhibit the degree of oxidation of molecules and cause these radicals to transform into inactive derivatives.

The non-enzymatic line of antioxidant defense includes low molecular weight molecules, such as glutathione, uric acid, vitamin A (retinoids), carotenoids, and beta-carotene, which has high antioxidant activity, as it traps free radicals. In addition, α-tocopherol (vitamin E), a fat-soluble free radical chain-breaking antioxidant, due to the presence of a hydroxyl group (-OH) in its structure, is an effective hydrogen donor. Ascorbic acid (vitamin C) acts as a hydrogen donor and reverses the oxidation process and can act both as an antioxidant and as a pro-oxidant (Jamillan et al. 2019). Bilirubin, lipoic acid, albumin, ferritin, ceruloplasmin, and transferrin also exhibit antioxidant properties and may indirectly reduce or inhibit the generation of reactive forms [11].

During pregnancy, disturbances in the oxidative-antioxidant balance and a deficiency of antioxidants can affect fetal development. The maternal status of antioxidant vitamins during

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pregnancy can impact fetal development [93]. It has been found that the antioxidant defense system is at a lower level in patients with spontaneous miscarriages compared to women who have not experienced miscarriages [94,95].

Hernández-Trejo et al. [96] showed an maternal obesity influences OS during pregnancy. The activity of SOD was higher in mothers with overweight/obesity compared to their children, but in mothers with normal weight SOD activity was smaller in their children. It was observed that maternal obesity influences OS and metabolism during pregnancy, thereby affecting the placenta and fetal growth, and that it may also impact the activation of the immune system.

5. Trace elements and oxidative stress

Trace elements form a non-enzymatic defense line against OS. They are components of antioxidant enzymes and participate in the enzymatic mechanism [97]. Their deficiency has been associated with increases in markers of oxidative damage, including DNA oxidation, protein oxidation, and lipid peroxidation.

5.1. Copper

Copper plays a vital role in maintaining overall health, including reproductive health [98,99]. It acts as an essential cofactor for numerous enzymes involved in metabolic reactions, angiogenesis, and oxygen transport. Copper also influences the proper functioning of metallothionein and glutathione, while affecting the activity of specific enzymes such as copper-zinc superoxide dismutase (Cu/ZnSOD), ceruloplasmin, catalase, and peroxidases. Inadequate copper levels in the body can lead to decreased enzyme activity, while excessive copper concentrations, characteristic of transition elements, can promote OS [100].

Recent studies have highlighted the impact of serum copper concentrations on complications in early pregnancy. Women with higher serum copper concentrations are more prone to experiencing complications during the first trimester compared to those with lower concentrations. Inadequate copper nutritional status impairs antioxidant mechanisms, whereas excessive concentrations stimulate the production of reactive oxygen species/reactive nitrogen species [101].

The precise relationship between copper and OS levels is not yet fully understood. A recent study by Rak et al. [102] revealed a negative correlation between OS levels in male newborns and the concentration of copper in maternal serum, which suggests a potential influence of copper on OS during pregnancy, emphasizing the need for further research in this area.

5.2. Iron

Iron (Fe), an essential element found in substantial amounts in the placenta, possesses the potential to induce OS by generating reactive oxygen species (ROS), which can cause damage to cells and tissues [100,103]. Acting as a catalyst in Fenton or Fenton-like reactions, Fe facilitates the conversion of ROS into highly reactive hydroxyl radicals (•OH) by reacting with hydrogen peroxide (H_2O_2) [104–106]. Consequently, Fe has the capacity to inflict various forms of oxidative damage to DNA, proteins, and cells.

In the context of pregnancy, Fe supplementation has been observed to heighten OS, as evidenced by increased levels of malondialdehyde (MDA) in the serum of mothers and the placenta [107]. Similarly to Cu, Fe serves as a crucial cofactor in essential processes like oxygenation, reduction reactions, and antioxidant metabolism [108]. Both Fe deficiency and excess during pregnancy have been linked to adverse outcomes for fetal development [109]. Notably, prenatal Fe supersaturation has been associated with an elevated risk of miscarriage, prematurity, low birth weight, and being small for gestational age (SGA), with OS identified as one of the potential underlying mechanisms [109].

In pregnant women without iron deficiency anemia (IDA), prophylactic Fe supplementation has been shown to induce OS and compromise the overall antioxidant capacity of the body [102,110].

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Specifically, Rak et al. [102] established a correlation between excessive Fe concentrations exceeding 400 μg/dL in the blood of pregnant women and elevated levels of OS in neonates.

5.3. Zinc

Zinc (Zn), an essential trace element, plays a pivotal role in various aspects of pregnancy, including embryogenesis, fetal growth, and development [111]. Inadequate Zn levels have been linked to adverse outcomes, such as reduced implantation rates, abnormal ovarian development, impaired ovarian follicular growth, compromised oocyte maturation, and increased risk of spontaneous abortions [112,113]. Maternal Zn deficiency during pregnancy also poses risks of low birth weight and infants being small for gestational age [114]. Furthermore, Zn deficiency has emerged as a potential risk factor for the development of preeclampsia [115].

Zn acts as an effective antiradical and anti-inflammatory agent. It forms chelates with sulfhydryl groups of proteins, providing protection against prooxidative processes. It shields cell membranes from peroxidation by displacing copper and Fe ions from their membrane binding sites [97]. Additionally, Zn plays a vital role in the synthesis of antioxidant enzymes and serves as a catalyst for several enzymes involved in lipid, carbohydrate, and protein metabolism. Notably, Zn, in conjunction with Cu, serves as a cofactor for Cu/Zn-superoxide dismutase (SOD), whose activity is compromised under Zn-deficient conditions [116].

Moreover, Zn exerts influence on the activity of other antioxidant enzymes. It displays catalytic functions for alkaline phosphatase and carboxypeptidase. By virtue of its antioxidative properties, Zn effectively hampers the generation of highly reactive hydroxyl radicals (•OH) and superoxide anions ($O2^{\bullet -}$). Furthermore, Zn actively participates in the synthesis, storage, and release of insulin, underscoring its crucial role in the pathogenesis of type 2 diabetes, atherosclerosis, and metabolic syndrome [117–119].

In the bloodstream, Zn primarily binds to albumin (60%) and transferrin (10%), with the remaining fraction existing in its free form. Maintaining adequate Zn levels is critical for preserving normal reproductive health, as diminished amounts have been associated with serious maternal-fetal consequences, including postpartum bleeding, fetal growth restriction, fetal malformations, preterm delivery, and preeclampsia [120].

Zn deficiency may contribute to OS by elevating lipid peroxidation levels due to diminished antioxidant defense mechanisms and compromised activity of Zn-dependent antioxidant enzymes, including Cu-Zn SOD [121,122]. Increased Cu/Zn ratios, resulting from imbalanced Cu and Zn levels, adversely impact the activity of antioxidant enzymes such as Cu/Zn SODs, ultimately leading to heightened lipid peroxidation and impaired antioxidant defense systems, which have been implicated in the pathogenesis of preeclampsia. Consequently, Cu/Zn ratios may serve as potential predictive markers for vascular complications in pregnancies affected by preeclampsia [123].

Numerous studies have investigated the effects of Zn supplementation on clinical manifestations and metabolic status in patients without intrauterine growth restriction (IUGR). It has been observed that Zn levels in women with moderate and severe IUGR were significantly lower compared to women without IUGR [124]. Considering that Zn intake protects trophoblast cells from mitochondrial OS and inflammatory markers, it may hold importance in the treatment of women with IUGR [125]. Therefore, Zn supplementation may serve as an appropriate adjunct therapy for pregnant women at risk of IUGR [125].

Furthermore, administration of Zn at a dosage of 30 mg/day for 6 weeks to patients with gestational diabetes mellitus (GDM) was found to have beneficial effects on metabolic profiles [126]. It should be noted that Zn was not identified as a causal mediator of the effects of other metals on OS [127].

5.4. Manganese

Manganese (Mn) is another essential element that plays a vital role in the synthesis and activation of various enzymes and in the regulation of glucose and lipid metabolism. It acts as an important cofactor for numerous enzymes, including the antioxidant manganese superoxide

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dismutase (Mn-SOD), which plays a role in protecting the placenta from OS by detoxifying superoxide anions [128]. Some studies suggest that low Mn levels may reduce the activity of Mn superoxide dismutase, leading to the accumulation of reactive oxygen species and the development of preeclampsia [129,130].

5.5. Selenium

Selenium (Se) is an essential trace element that plays a critical role in the synthesis and function of endogenous antioxidants, such as glutathione peroxidase (GPx), selenoprotein P, thioredoxin reductase (TrxR), and iodothyronine deiodinases (IDD) [131]. It exerts control over the antioxidative activity of the enzymatic glutathione system [132], acts as an antioxidant, supporting both humoral and cell-mediated immunity, and is significant for reproductive processes [133].

Dietary Se is primarily bound to amino acids as selenocysteine and selenomethionine. In organs such as the spleen, liver, serum, and blood, selenates (VI) undergo reduction to selenites (IV) or hydrogen selenide (H_2Se). Selenates in the IV oxidation state exhibit higher tissue affinity, forming complexes with proteins and displaying enhanced incorporation into glutathione peroxidases (GPxs). Enzymatic activity of GPxs increases with elevated Se concentrations [134]. These compounds possess the capability to traverse the blood-placenta barrier, thereby reaching the fetal compartment. Throughout pregnancy, there is a gradual decline in Se concentration due to increased placental transport and transfer to breast milk [135]. Studies have suggested that Se deficiency is associated with various pregnancy disorders, including miscarriage, pre-eclampsia, gestational diabetes mellitus, pregnancy-induced hypertension, neural tube defects, fetal growth restriction, and preterm birth [136–140]. Se deficiency, especially in the second trimester, has been found to the production of OS and an increase in inflammatory mediators [141], affecting the risk of developing pregnancy disorders by reducing placental GPX activity and impeding the function of other selenium-dependent antioxidants, including thioredoxin reductases (TXNRD), thereby leading to placental OS [142]. To optimize the antioxidative potential of GPX, serum Se levels should ideally reach approximately 100 µg Se/L [143]. Levels falling below this threshold in pregnant women may detrimentally affect fetal growth.

Supplementation with Se has demonstrated the ability to enhance cell proliferation, mitigate DNA damage, and attenuate apoptosis under normal conditions or in the presence of OS [144]. Administering Se during pregnancy holds promise in reducing maternal OS and yielding beneficial effects for both the mother and fetus [145]. Reported benefits of Se supplementation encompass a reduction in the incidence of pre-eclampsia/pregnancy-induced hypertension (PE/PIH), gestational diabetes mellitus (GDM), intrauterine growth restriction (IUGR), preterm premature rupture of membranes (PROM), postpartum depression, and postpartum thyroid dysfunction. Furthermore, Se supplementation may influence breast milk composition, fetal lipid profile, and fetal bilirubin levels, although it had mixed outcomes among HIV-positive mothers and their newborns [145].

Studies conducted on Iranian women from Arak reported favorable effects of Se supplementation on OS in pregnant women but did not observe reductions in the incidence of PE, FGR, and preterm birth [146–148]. That observation may be attributed to the small sample size of the studies conducted, and it should be noted that women from the Arak region may have higher Se concentrations compared to women from other regions of Iran.

Currently, the underlying mechanisms concerning the role of Se and Se-dependent enzymes remain unclear. Additionally, the optimal dosage, timing, and duration of Se supplementation during pregnancy are still subjects of ongoing debate and investigation [149].

6. Potential biomarkers of oxidative stress

Direct determination of reactive oxygen species (ROS) concentrations poses challenges due to their short half-lives. As a result, protein markers are employed to assess the extent of redox imbalance. These OS markers encompass molecules that undergo modifications as a consequence of ROS interactions, as well as components of the antioxidant system that undergo changes and modifications in response to stress conditions [150]. The selection of an OS marker relies on specific

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criteria, including its specificity, sensitivity to elevated ROS levels, temporal stability enabling sample collection and analysis, and result reproducibility [151].

DNA, lipids (including phospholipids), proteins, and carbohydrates exemplify molecules susceptible to *in vivo* modifications induced by excessive ROS levels [151]. Hence, indirect assessment of ROS levels by examining oxidative damage to lipids, proteins, and nucleic acids within cellular systems presents a promising alternative for evaluating OS in clinical samples. An array of markers is employed to describe OS, encompassing malondialdehyde (MDA), nitric oxide (NO), reactive oxygen species (ROS), total antioxidant capacity (TAC), total antioxidant activity (TAA), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione peroxidase-4 (GPx4), glutathione reductase (GR), lipid peroxidation (LPO), 8-hydroxydeoxyguanosine (8-OHdG), oxidized glutathione (GSSG), catalase (CAT), superoxide (O_2^-), paraoxonase (PON-1), oxidative stress index (OSI), high-sensitivity C-reactive protein (hs-CRP), 8-iso-prostaglandin F2α (8-iso-PGF2α), prostaglandin F2α (PGF2α), glutathione (GSH), and glutathione transferase (GST). These markers are analyzed using various materials, primarily blood (serum or plasma) and placenta, along with urine, Wharton's jelly mesenchymal stem cells derived from the umbilical cord, and saliva [152,153].

Biomarkers of OS are employed in monitoring studies to indirectly assess pregnancy complications [154]. Lipid peroxidation (LPO) serves as an indicator of OS severity in cells and tissues. Several factors contribute to increased LPO intensity, including elevated circulating lipoprotein levels, prooxidative activity of the placenta, and altered basal metabolism during pregnancy [155].

Among the markers used to evaluate lipid peroxidation, malondialdehyde (MDA), a low-molecular-weight aldehyde resulting from the breakdown of polyunsaturated fatty acids, is widely utilized [156]. Laboratory quantification of MDA involves its reaction with thiobarbituric acid, providing a measure of OS. As a secondary product of lipid peroxidation, MDA exerts cellular toxicity and can interact with DNA and proteins, often leading to mutagenesis. Additionally, MDA exhibits potential atherogenic properties. The ideal concentration of MDA in the blood serum of healthy individuals ranges from 0.32-53.8 nmol/mL; however, the genotoxicity associated with this lipid peroxidation product should be considered [157]. Notably, physiological cellular metabolism can lead to endogenous MDA production, and its concentration is significantly influenced by factors such as diet, physical activity, and sample storage conditions [157]. Mentese et al. [158] demonstrated the high sensitivity of MDA as an indicator of neonatal hypoxia. Numerous studies have reported elevated MDA levels in serum, plasma, and placental tissue samples of preeclamptic women [159]. Rudra et al. [160] observed a correlation between high plasma MDA concentration and the occurrence of preeclampsia.

F2-isoprostanes, particularly 8-iso-prostaglandin F2α (8-iso-PGF2α), are considered the most reliable *in vivo* indicators of lipid peroxidation. 8-iso-PGF2α is enzymatically generated through the prostaglandin endoperoxide synthase pathway. Extensive research involving nearly 500 animal studies and 900 human studies has demonstrated correlations between 8-iso-PGF2α and various diseases and exposures. Importantly, 8-iso-PGF2α differs from its enzymatic lipid peroxidation analog [161].

Superoxide dismutase (SOD) serves as an example of an antioxidant system molecule that undergoes alterations and modifications in response to OS. Its concentration in the blood serum of healthy individuals is approximately 4,315 U/mg. OS induces a sharp increase in SOD synthesis. Conversely, low or reduced SOD activity is associated with an elevated risk of OS-related pathological states [162]. Hernández-Trejo et al. [96] demonstrated higher levels of SOD, arginase, carbonylated proteins (CP), and nitrites in umbilical cord blood samples compared to maternal blood samples. In contrast, levels of glutathione peroxidase (GSH-Px), malondialdehyde (MDA), lipid hydroperoxides (LOOH), and free fatty acids (FFA), in contrast to the levels of glutathione peroxidase (GSH-Px), malondialdehyde (MDA), lipid hydroperoxides (LOOH), and free fatty acids (FFA) which were lower in newborns compared to their mothers. This may indicate a buffering role of OS by the placenta, and suggests the involvement of various factors that influence the redox balance, as mentioned several times before.

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HIF1A serves as an indicator of hypoxia and plays a role in cellular response to OS. Ashur-Fabian [163] found that maternal serum mRNA levels of HIF1A may reflect the hypoxic state during pregnancy, while HIF1A levels in the placenta better represent fetal hypoxia. Zhang et al. [164] observed significantly higher mRNA levels of HIF1A in the placenta of monochorionic twins with intrauterine growth restriction, particularly in fetuses with restricted growth.

Verit et al. [165] suggest that total oxidant status and total antioxidant status levels can serve as additional markers for diagnosing and assessing the clinical severity of nausea and vomiting of pregnancy. Additionally, based on an analysis of literature data, Drejz et al. [152] recommend the establishment of a common core panel of OS markers to be used in all studies related to OS in obstetrics and gynecology. They propose including reactive oxygen species (ROS) as a direct marker of OS, 8-hydroxydeoxyguanosine (8-OHdG) as a marker of DNA/RNA damage, and malondialdehyde (MDA) as a marker of lipid peroxidation. They also suggest incorporating two commonly used antioxidant parameters, total antioxidant capacity (TAC) and glutathione (GSH), into the core panel of tests.

The monitoring of *nutrition* during *pregnancy* is important to prevent nutritional imbalances and deficiencies in important *micronutrient deficiencies [141].*

7. Research on animal models

Due to the limitations in conducting direct studies in pregnant women, many research investigations are carried out using animal models. For example, Xu et al. [166] demonstrated the significant pro-oxidative effects of lipopolysaccharide (LPS) in the amniotic fluid during embryonic development of rats. LPS exerted a substantial influence on the occurrence of external fetal abnormalities, intrauterine growth retardation, and fetal death. Substantiating the impact of OS, administration of an antioxidant effectively mitigated these effects.

Studies conducted in calves have indicated that caesarean section leads to increased OS, characterized by elevated levels of malondialdehyde and reduced catalase activity. This phenomenon results in lipid peroxidation and subsequent tissue damage [167].

Furthermore, the embryos of diabetic rats exhibit heightened free oxygen radical activity, which is believed to underlie the teratogenicity associated with diabetic pregnancies [168,169].

Guo et al. [170] investigated the effects of catalase supplementation on the activity of antioxidant enzymes and reproductive performance in sows and their offspring. Their findings demonstrated that administering catalase reduced the incidence of intrauterine growth restriction (IUGR) and improved antioxidant capacity in both sow serum and piglet umbilical cord samples.

Viana et al. [171] provided evidence of oxidative DNA damage in rat embryos affected by diabetes, linking this mechanism to the teratogenic effects observed in the fetus. Chronic OS was found to contribute to a higher frequency of fetal resorption in rat models [172]. Cederberg and Eriksson [173] suggested that catalase may play a protective role against diabetic embryopathy in rats, while reactive oxygen species (ROS) are implicated as mediators of this teratogenic process. Similarly, Sivan et al. [174] demonstrated, in a rat model, that the excessive oxidative burden observed in diabetic pregnancies can result in embryopathy and tissue damage.

Supplementation with Se and Cr shows promise in preventing the development of gestational diabetes mellitus (GDM) by alleviating endoplasmic reticulum stress in the liver.

Studies utilizing laboratory animals have also indicated that zinc gluconate supplementation may improve symptoms and pregnancy outcomes in preeclampsia by mitigating OS and modulating the balance of systemic inflammatory responses and angiogenic factors [175].

8. Conclusion

The available scientific literature provides compelling evidence for a plausible association between compromised antioxidant enzyme activity and the occurrence of adverse pregnancy outcomes. OS exerts detrimental effects on maternal physiology, pregnancy progression, and fetal development by disrupting placental function and compromising oxygen and nutrient delivery to the developing fetus. This oxidative imbalance can contribute to miscarriages, fetal developmental

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abnormalities, preterm birth, and low birth weight. Consequently, it is crucial to further explore this field of research, particularly in conjunction with comprehensive investigations into the interplay of micronutrients and macronutrients. This should advance our understanding of the underlying mechanisms and enable the development of effective interventions to mitigate the detrimental effects of OS during pregnancy.

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