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Review article

Oxidative stress in pregnancy complicated by preeclampsia

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ABSTRACT

Preeclampsia is a multisystemic disorder of pregnancy that causes perinatal morbidity and mortality. Studies published in the last decade have contributed to a better understanding of physiopathogenesis through key mechanisms involved, such as altered immune response, endothelial dysfunction, oxidative stress and systemic inflammatory response, as well as genetic susceptibility. Oxidative stress (OS) plays an important role in the development of preeclampsia, since it alters placental remodeling and placental vascular endothelial dysfunction, resulting in an ischemia/reperfusion injury with an increase in xanthine oxidase activity that produces high levels of reactive oxygen species (ROS). ROS can be generated through many pathways within cells, mitochondria, endoplasmic reticulum (ER) and enzymes such as NADPH oxidase are the most important sources, causing widespread and indiscriminate damage to cells and tissues, which leads to an intravascular inflammatory response and maternal systemic endothelial dysfunction characteristic of this prenatal syndrome. Therefore, the following review aims to identify the main risk factors and the role of OS as a pathophysiological mechanism in the development of preeclampsia.

1. Introduction

Preeclampsia is a multi-systemic disorder that occurs in pregnancy, characterized by hypertension and proteinuria from the twentieth week of gestation. It represents one of the main causes of maternal morbidity and mortality such as strokes, liver breakage, pulmonary edema or kidney failure; as well as perinatal such as premature birth, intrauterine growth restriction and fetal death.

According to reports in the last decade, preeclampsia is associated with pathophysiological changes with the presence of placental insufficiency, high levels of OS, a generalized inflammatory state, and endothelial dysfunction characteristic of this prenatal syndrome. In the placenta, the OS resulting from ischemia-reperfusion injury is involved in the pathogenesis of preeclampsia.

2. Pregnancy

Pregnancy is a dynamic and anabolic state; a series of complex events that include decidualization, placentation and childbirth [1–3]. Within several weeks of conception, a new endocrine organ, the placenta is formed and secretes hormones that affect maternal and fetal metabolism until delivery. In addition to the changes in the mother's anatomy and physiology, fetal growth and development are maintained from: 1) accretion in new tissue or deposition in maternal stores, 2) redistribution between tissues, and 3) increase of metabolic rate [4].

During pregnancy, supplemental energy is required for fetal growth, placenta and maternal tissues. The average additional energy cost of a pregnancy has been calculated at 80,000 kcal for a period of 9 months, which leads to the gradual increase in oxygen consumption [5]. Since the production of many different hormones increases during pregnancy, including thyroxine, cortico-adrenal and sex hormones, the mother's basal metabolism rises by 15% during the second half of pregnancy, and at birth oxygen consumption is usually 20% above normal [6].

Pregnancy is a state of metabolic challenge to the mother and the developing fetus, accompanied by a high energy demand and an increase in oxygen requirements, as well as a high mitochondrial activity, having the placenta as a key source of this operating system. Intrauterine OS during pregnancy is a physiological response to the demands of fetus-placental energy; a burst of oxidative stress in the placenta is observed when oxygen tension increases three times in the intervillous space with the onset of maternal blood flow at the beginning of the second trimester. The ability of placental antioxidant

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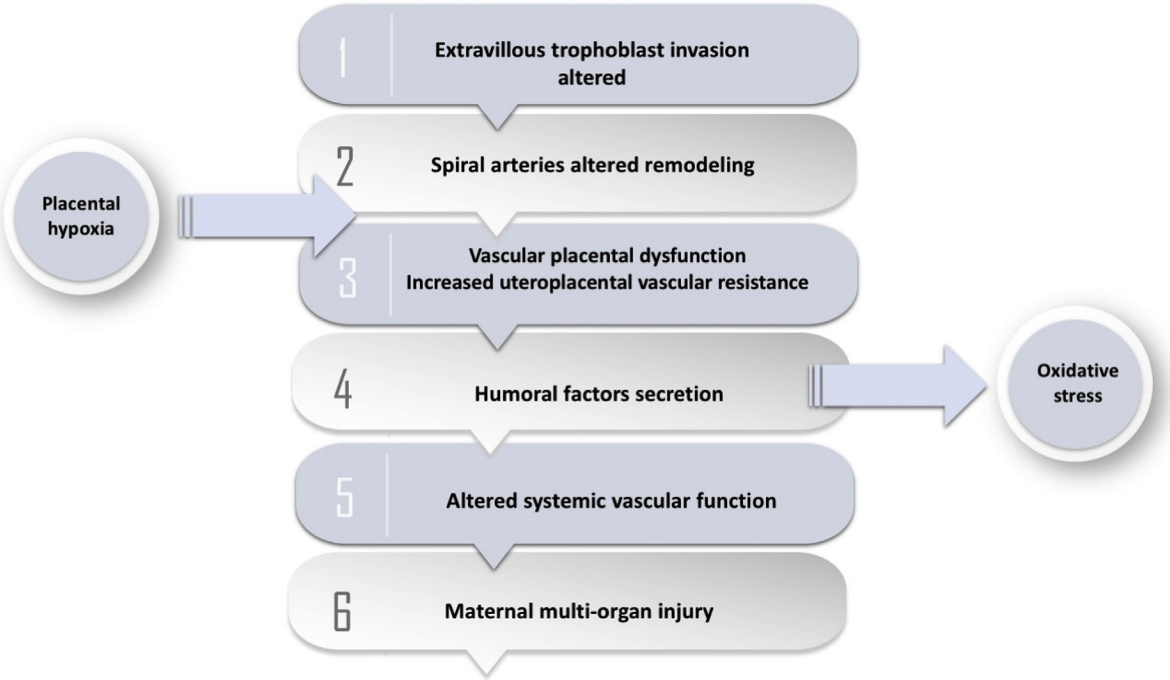

Fig. 1. Physiopathogenesis of preeclampsia. 1, 2. Poor placentation leads to placental hypoxia. 3, 4. The hypoxic placenta leads to vascular dysfunction and the secretion of humoral factors in the maternal systemic circulation and secondarily the 5. Alteration of the maternal systemic vascular endothelial function, which eventually produces 6. Multiple organic insufficiency.

defenses to reduce the effects of potentially harmful reactive oxygen species (ROS) is essential for healthy placental function and optimal growth and development of the fetus [7]. The generation of ROS is an intrinsic result of aerobic energy, but the process is well balanced in healthy pregnancy by redox enzymatic and non-enzymatic antioxidant systems [8].

2.1. Normal placentation and the role of nitric oxide in pregnancy

The most important function of the placenta is the exchange of nutrients and oxygen between a mother and her fetus. This exchange takes place at the interface of the placental villi with its vascular membranes and the intervillous space in which the maternal blood flows. This process allows the fetus to grow and develop normally. To determine that a placenta works properly, placentation must occur with a remodeling of the spiral arteries by extravillous trophoblast (EVT) [9]. ROS are important signal transducers in normal placentation. Low oxygen tension in early pregnancy is also an important promoter of placental angiogenesis [10,11].

In early pregnancy, the remodeling of the spiral arteries begins immediately after implantation of the blastocyst with the invasion of EVT cells in the decidua and one third of the thickness of the myometrium; these cells destroy the media and transform the spiral arteries of the vessels of narrow diameter into other larger in diameter, allowing an adequate perfusion of the placenta and the formation of a continuous layer in the maternal-placental interface. In the first trimester, the embryo develops in a low oxygen environment allowing the proliferation of trophoblastic cells. The uterine arteries also change during the first weeks of pregnancy and, subsequently, the hemochorial placentation converts the spiral arteries into a chamber of high flow and low velocity. This phenomenon results in a change from low oxygen tension to higher oxygen tension in the intervillous space at the end of the first trimester, which entails a significantly greater exchange of oxygen at the placental level to meet the needs of the fetus in growth [12–17]. Between weeks 8 and 12 of gestation, oxygen tension rises sharply in the maternal arterial circulation from less than 20 to more than 50 mm Hg, which leads to a period in which the tissue's response to changes in oxygen concentration can play a key role in the success or failure of pregnancy [6].

The physiological changes in normal pregnancy include adaptations in the circulatory system: a) 30–40% increase in cardiac output (due to a high heart rate and systolic volume) b) a 40–50% increase in plasma volume c) decrease in blood pressure to maintain homeostasis [18]. Nitric oxide (NO) contributes to the maintenance of vascular tone to increase uterine blood flow. Endothelial-dependent vasodilation is partly mediated by NO and is positively regulated during pregnancy due to the increase in estrogen levels. Endothelial cells produce NO, which is a potent steam-relaxing and anticoagulant factor. The activation of NO synthase (NOS) triggers the production of NO during pregnancy. The endothelial nitric oxide synthase isoform (eNOS) is constitutively expressed in the vascular endothelium and maintains vascular tone through intrinsic NO synthesis, thus inhibiting the adhesion of leukocytes and platelets to the endothelium, which prevents the pro-inflammatory state. In contrast, inducible NOS (iNOS) is stimulated in inflammatory or proinflammatory state and produces temporary surplus of NO. NO dysfunction derived from the endothelium has been implicated as a possible cause of preeclampsia [19,20].

2.2. Etiology

The etiology and pathogenesis of preeclampsia are still little known. In the last decade, promising studies have been carried out that report substantial progress in the understanding of the pathophysiology of preeclampsia. Theories have been proposed with a common theme, that of endothelial cell dysfunction. Among the factors that support these theories are: environmental, poor trophoblastic invasion, vascular and angiogenic factors, oxidative stress, genetic and immunological factors. The etiopathogenic mechanism of preeclampsia is summarized in a model consisting of two stages: 1) alteration in placental perfusion, 2) endothelial dysfunction or maternal syndrome and the role of oxidative stress as a common factor between the two-stage model (Fig. 1). Finally, the existence of four possible pathophysiological responses of

Table 1
Risk factors for the development of pre-eclampsia.
Modified from Chaiworapongsa et al., 2014.

First pregnancy
Maternal age (< 20 or > 35 years old)
Pre-eclampsia/eclampsia in the previous pregnancy
Multiple gestation
Obesity
Pre-eclampsia family history (mother, sister)
Pre-existing diseases
o Chronic arterial hypertension
o Renal impairment
o Infertility
o Thrombophilias (anti phospholipid antibody syndrome)
o Autoimmune diseases
o Diabetes Mellitus type 1 and 2
Limited contact with sperm
Assisted reproduction techniques
Paternal genetics
Molar pregnancy

preeclampsia is proposed: a) poor immune adaptation, b) placental ischemia, c) oxidative stress and d) genetic susceptibility [21–23].

2.3. Predisposing factors of preeclampsia

There are established predisposing factors for the development of pre-eclampsia; the risk depends on the individual factor and the accumulation of associated factors (Table 1). The risk of developing pre-eclampsia and the degree of severity may increase up to 9 times with a history of preeclampsia in a previous pregnancy. Other risk factors that increase the probability of preeclampsia with severe manifestations include diabetes, hypertension, multiple pregnancies, African-American background, pre-existing diseases, history of thrombophilia, assisted reproduction, and obesity [14,24].

The extreme of maternal age at first conception is of the utmost importance (under 20 and over 35 years old). Preeclampsia is usually more common in nulliparous women, probably by an immune mechanism, given the limited exposure to sperm that contributes as a risk factor for the patient to develop preeclampsia. A higher risk of pre-eclampsia is observed in pregnancy after artificial insemination or in multiparous women who change partners [14,25]. Males who have generated a complicated pregnancy with preeclampsia are a risk factor for a new partner to develop the complication in a future gestation (paternal genetics) [14,26,27].

2.4. Pathophysiology of preeclampsia

After the EVT in the placenta invades the maternal decidua, spiral arteries undergo a remodeling process accompanied by the replacement of arterial smooth muscle and elastic tissue with fibrinoid material; the above causes a reduced remodeling of maternal spiral arteries that eventually result in a decreased blood flow to the placenta [28,29]. The proper development of trophoblast cells and uterine vessels is a key condition for successful human pregnancy. Once attached to the endometrium, trophoblastic cells proliferate rapidly and the outer layer fuses to form multinucleated syncytiotrophoblasts (STB), while an internal group of cells becomes invasive EVT that soon extend to the uterine stroma. According to the “two-wave invasion” theory, this type of invasion can be relatively preliminary within the deciduous layer and is followed by a pause until about the 12th week of human gestation when a second wave of deep and diffuse invasion begins [30,31]. The remodeling of the maternal spiral artery begins directly after implantation of the blastocyst with the invasion of EVT cells in the decidua and the formation of a continuous EVT shell in the maternal and placental interface [32]. When EVT cells cannot invade the spiral arteries, incomplete plugging and fragmentation of the EVT envelope occurs. This leads to a premature onset of maternal placental circulation and, consequently, to a premature increase in oxygen tension that translates successively into a relative hyper-toxic environment. The increase in oxygen tension leads to the formation of ROS [33]. The syncytiotrophoblast is especially sensitive to ROS because this layer lacks sufficient concentrations of antioxidant enzymes such as manganese superoxide dismutase (Mn-SOD) [34]. In addition, this layer is the first line of fetal cells that find maternal blood rich in oxygen, being exposed to the highest levels of oxygen and increasing their cell vulnerability to ROS [31]. A deficiency in the invasion of trophoblast, especially the second wave, is associated with the development of preeclampsia. A mass of reactive oxygen species inactivates biomacromolecules (complex cellular molecules such as lipids, proteins, and nucleic acids), leading to lipid peroxidation, the oxidation of amino acid residues (especially cysteine residues), the formation protein – protein cross-linking of proteins and DNA oxidative damage [35]; and alters cellular metabolism, resulting in endothelial dysfunction and excessive apoptosis of the trophoblast, as well as an increase in anti-angiogenic soluble fms-1 type (sFlt-1) tyrosine kinase receptor and soluble endoglin (sEng) bind and neutralize the circulating proangiogenic vascular endothelial growth factor (VEGF) and transforming growth factor-β1 (TGF-β1), respectively [28,36–38]. Reactive oxygen species, products of chronic hypoperfusion and low oxygen level in the first trimester, boost VEGF expression through hypoxia-inducible factor 1 (HIF-1), a transcription factor that adapts to hypoxidosis, but the high level of oxygen then decreases the VEGF [39]. Placental growth factor (PlGF) appears to be regulated in the opposite direction, being present at a low level during a low level of oxygen and increasing along with the elevation of the oxygen concentration. Therefore, premature hemoperfusion and hyperoxia in early pregnancy can lead to reduced levels of VEGF and a premature peak of PlGF, which can cause poor development of the villous vessels and pregnancy failure [39,40]. In conclusion, in preeclampsia an abnormal remodeling of the spiral arteries is observed, which leads to placental hypoperfusion and systemic endothelial dysfunction [41]. The biomacromolecules lesion due to the increase in reactive oxygen species alters cellular metabolism, which leads to endothelial dysfunction and excessive apoptosis of the trophoblast; placental dysfunction leads to an imbalance in circulating pro-angiogenic or antiangiogenic factors, especially PlGF, sFlt-1 and a truncated form and soluble VEGF, which neutralizes VEGF and PlGF [42]. Increased levels of sFlt-1 and reduced levels of PlGF can be used to predict the subsequent development of PE; serum concentrations of s-Flt-1 increase, while PlGF concentrations decrease, resulting in an increase in the s-Flt-1/PlGF ratio [43,44]. These abnormalities in the infusion of the placenta, activate or repress the normal functions of the endothelial cells, end in an altered remodeling and the deficient development of the placenta caused by superficial trophoblastic invasion [45,46]. Poor placental perfusion due to irregularities in the placental process and trophoblast invasion during the development of the placenta has been associated with hypertension in the early stages of pregnancy [47]; subsequently it is associated with the onset of preeclampsia and generalized maternal endothelial and vascular dysfunction [48]. Several investigations support the theory that preeclampsia is a syndrome consistent with vascular endothelial dysfunction induced by factors released from an ischemic placenta [49,50].

Reduced placental perfusion modifies the placental environment: reactive oxygen species and the activation of endothelial cells through different mechanisms result in the development of endothelial dysfunction (Fig. 1). Due to the defective invasion of the trophoblast, intermittence of arterial blood flow occurs, which causes periods of ischemia/reperfusion, creating a hypoxic environment that favors OS, the consequent oxidative damage and generalized inflammation characteristic of preeclampsia [28,51–53]. On the other hand, the interaction between NO and reactive oxygen species modulates vascular tone; therefore, the altered balance of NO and EROs also seems to play a critical role in the pathogenesis of preeclampsia [54].

2.5. Oxidative stress in the pathogenesis of preeclampsia

During normal pregnancy, the generation of reactive oxygen species increase as a result of oxidative stress and are necessary for an adequate physiology of pregnancy [55]. Oxidative stress is the imbalance between the ROS prooxidant species and the antioxidant defense that operate in tissues [6,56–58].

The first line of defense against ROS is the enzymatic antioxidant system: superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) that metabolize these reactive species into innocuous by-products. The second line corresponds to the non-enzymatic antioxidant system: vitamins C and E, α tocopherol, β-carotene, ubiquinone, carotenoids, ascorbic acid, uric acid and glutathione; they work by reducing and inactivating free radicals and oxidants [3,59].

The placenta contains low concentrations and activity of antioxidant enzymes during the first trimester that include CAT, GPx and Cu/Zn and Mn-SOD; thus trophoblastic cells are particularly susceptible to oxygen-mediated damage [60]. Therefore, when oxygen tension triples in the intervillous space with the onset of maternal blood flow at the beginning of the second trimester, a burst of OS is observed in the placenta. This oxidative lesion alters remodeling and placental function, which affects the subsequent course of pregnancy [61,62].

OS is relevant to the pathophysiology of preeclampsia since it induces the release of proinflammatory cytokines and chemokines, as well as the trophoblast residues. Pre-eclampsia is characterized by an inflammatory response resulting from ischemia and re-perfusion [8,60]. Placental re-perfusion injury converges on a harmful inflammatory response that is responsible for inflammation and damage by OS. Immediately after the placental re-perfusion injury, the restored blood flow releases cytokines and other inflammatory factors, and harmful levels of ROS such as the superoxide radical, in response to these events. Scientific evidence suggests that reduced perfusion due to aberrant placentation and superficial invasion of trophoblast triggers a placental oxidative stress condition that leads to an intravascular inflammatory response and endothelial dysfunction (Fig. 2) [28,63]. Increased exposure to ROS causes carboxylation of proteins, lipid peroxidation and DNA oxidation, which has been observed in placentas of patients with preeclampsia [6,62]. In addition, the degree of OS seems to be related to the severity of preeclampsia [10].

2.5.1. Reactive oxygen (ROS) and nitrogen (RNS) species and enzymatic involvement in the pathogenesis of preeclampsia

Oxygen is the final acceptor of electrons generated in different metabolic processes, being the most relevant activity of oxidases (xanthine oxido-reductase; NADPH (nicotinamide adenine dinucleotide phosphate) oxidase), nitric oxide synthase (NOS) and the mitochondrial oxidative phosphorylation process. Reactive oxygen species such as superoxide anion ($O_2^{\bullet-}$) (product of the reduction of an oxygen electron), the reduction of oxygen with 2 or 3 electrons leads to the formation of hydrogen peroxide (H_2O_2) and the hydroxyl radical ($OH^{\bullet}$); as well as the RNS: nitric oxide (NO), and peroxynitrite ($ONOO^-$) (union between NO and superoxide anion), are signaling molecules that regulate many functions in human physiology. ROS signaling is directly controlled by the host's defenses, the antioxidant system, which eliminates the actions of these species. The main inhibitor of superoxide is the antioxidant SOD that converts it into hydrogen peroxide (H_2O_2) and water. The H_2O_2 is immediately neutralized by CAT. Iron and other metals catalyze the production of a potent, more injurious pro-oxidant species called $OH^{\bullet}$ through the Fenton reaction. ROS and RNS have short half-lives and react with affected molecules such as proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), carbohydrates or free fatty acids by altering their structure and/or function [28,50,58,58,64–68].

Ischemic placenta in preeclampsia induces the production of ROS, which occurs in the systemic vasculature in the second stage of the pathogenesis of preeclampsia [69]. In some studies, hydrogen peroxide production and increased levels of malondialdehyde (end product of lipid peroxidation) have been found in women with preeclampsia [70,71]. Excessive iron levels and a decreased unsaturated iron-binding capacity are factors associated with OS and contribute to the pathogenesis of preeclampsia/eclampsia [72].

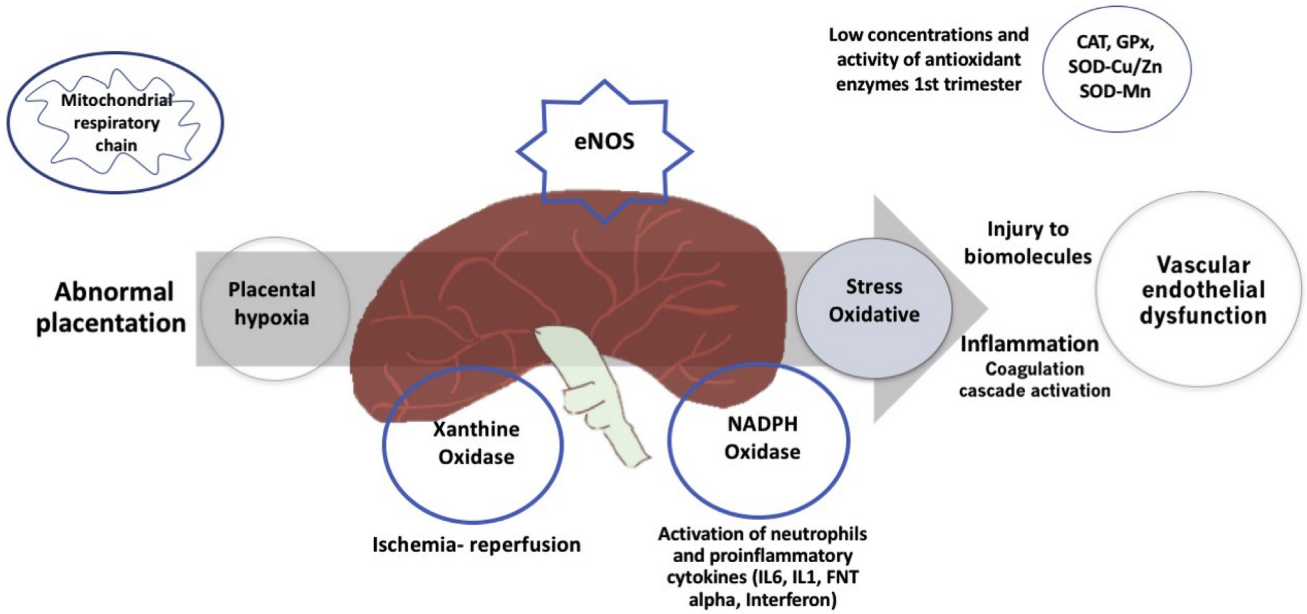

Fig. 2. Oxidative stress in the pathogenesis of preeclampsia. The main sources of reactive oxygen and nitrogen species are schematized. Mitochondria, endoplasmic reticulum, xanthine oxidase, NADPH oxidase; the latter generates the $O_2^{\bullet-}$ by transferring electrons from NADPH into the cell through membrane and coupling them to O2. When the intracellular production of ROS increases (especially $O_2^{\bullet-}$), NO can react with ROS to form $ONOO^-$ causing decoupling of eNOS. When the first line of defense against ROS, the enzymatic antioxidant system: SOD, GPx and CAT is insufficient to maintain homeostasis, oxidative damage is generated in the placenta causing inflammation and the release of cellular debris in the maternal circulation, oxidative stress seems to be the central component of placental and endothelial dysfunction, the causative etiology of preeclampsia. Modified from Ref. [50].

2.5.2. Mitochondrial respiratory chain

The mitochondrion is a very important organelle since it is responsible for the production of ATP through respiration and regulates cellular metabolism. Mitochondrial activity is essential in pregnancy because it maintains the metabolic activity of the placenta throughout this period [73]; likewise, mitochondria are another source of superoxide radical formation that contributes to placental damage. The generation of ROS is the result of mitochondrial activity in the presence of hyperoxia ("leakage" of electrons to molecular oxygen to generate the reactive superoxide ion) or hypoxia (electron accumulation) [10,74–76]. Beyond its role as a source of OS, it is known that mitochondria are affected by exposure to suboptimal environmental conditions. Mitochondrial dysfunction has been a key factor for fetal programming in situations of placental insufficiency such as that developed in preeclampsia [73].

After reperfusion injury, reoxygenation induces tissue and mitochondrial damage. As in other vascular diseases, mitochondrial dysfunction is also identified in preeclampsia [77]. Some sources of O · formation in mitochondria under pathological conditions include complexes I and II of the mitochondrial transport chain [69,74]. The involvement of the mitochondrial electron transport chain (METC) in early pregnancy is unclear. However, the mitochondrial mass in the placenta increases with gestational age, which suggests a greater contribution of METC to the generation of ROS in placental pathologies such as preeclampsia [78,79]. Changes in preeclamptic placental proteome, related to the respiratory chain and the generation of ROS, can explain the importance of mitochondria in the development of preeclampsia [80]. Therefore, mitochondrial function is altered in hypoxic placentas [81]. Beyond its role as a source of oxidative stress, it is known that mitochondria are affected by exposure to suboptimal environmental conditions such as preeclampsia. Placental metabolism is maintained during pregnancy by increasing biogenesis and mitochondrial activity [73].

2.5.3. Endothelial nitric oxide synthase (eNOS)

Catalysis of guanidino nitrogen from L-arginine by NOS results in the production of gaseous NO. Three main NOS isoforms have been identified: neuronal (nNOS or NOS1), inducible (iNOS or NOS2) and endothelial (eNOS or NOS3); they are present in the endothelium, nervous system, immune cells and, in pregnancy (fetal trophoblast). Increases in systemic and uteroplacental NO have been reported in normal pregnancy, and tend to be reduced in animal models of preeclampsia (reduced uterine perfusion) [18].

The role of NO in maintaining systemic blood pressure against the increase in cardiac output and plasma volume depends on its bioavailability to the adjacent vascular endothelium. ROS such as superoxide anion, exerts significant tissue damage in the placenta, reacts with NO to produce $ONOO^-$, a potent pro-oxidizing agent. High levels of $ONOO^-$ oxidize and damage DNA, proteins and lipids [18,82]. In addition, $ONOO^-$ induces decoupling of eNOS by oxidation of tetrahydrobiopterin (BH4) and compromises the activity of eNOS [83,84]. In addition, $ONOO^-$ can lead to irreversible nitration of tyrosine residues in other proteins, causing altered phosphorylation and enzymatic dysfunction. The $ONOO^-$ formation not only inhibits the bioavailability of NO but also the production of prostaglandin I2 (PGI2) by tyrosine nitration and inhibition of prostaglandin synthase (PGIS) that causes smooth muscle contraction and activation of platelet and white blood cells [69,85]. Increasing asymmetric dimethyl-L-arginine (ADMA) can inhibit eNOS activity by decoupling of eNOS and reducing the uptake of L-arginine in endothelial cells. Both changes decrease the generation of NO induced by eNOS. In addition, the increase in plasma ADMA is associated with the increase in oxidative stress and endothelial dysfunction. This decoupling could play a critical role in the pathogenesis of preeclampsia due to endothelial dysfunction [19,20]. In summary, taking as reference that the NO plays an important role in the development and remodeling of the placental and uterine vasculature; the bioavailability of NO, which is altered by the ROS and the metabolite $ONOO^-$, deteriorates vascular function and reduces placental perfusion, causing an alteration of the fetoplacental signaling of the maternal organism [18].

2.5.4. Xanthine oxidase

Early onset preeclampsia associated with impaired vascular remodeling of the spiral arteries and invasion of superficial trophoblast. The preservation of the muscular layer of the spiral arteries results in an intermittent placental perfusion that cause repeated hypoxia/reoxygenation, which significantly affects the placenta in pregnancy [36,48]. Ischema/placental reperfusion represents a notable stimulus for the conversion of xanthine dehydrogenase to xanthine oxidase. The activity of endothelial xanthine oxidase leads to increased production of superoxide and peroxide, which induces cellular damage, immune activation and vascular dysfunction, such as impaired endothelial-dependent vascular relaxation in women with preeclampsia [3,6,69,70].

In preeclampsia, the generation of $O2^{\bullet-}$ by xanthine oxidase (XO) has been show in placental reperfusion injury. Dependent dehydrogenase nicotinamide adenine dinucleotide (NAD) can be transformed under various pathophysiological conditions, such as hypoxia or cytokine stimulation, into an oxygen-dependent form of oxidase. XO catalyzes the oxidation of xanthine to uric acid, accompanied by the production of superoxide. As preeclampsia is characterized by hyperuricemia, XO is the uncontrolled source of ROS production when the concentration of its oxidase form increases [86–88]. Studies have shown that cells of cytotrophoblast, villous trophoblast, stroma and endothelial cells of preeclamptic women, increase the activity of xanthine oxidase [89,90]. Subsequently, increased mRNA expression of XO in villous endothelial cells and extravillous trophoblast accompanied by decreasing the expression of SOD in the same cells, are described in preeclamptic women [86,89].

2.5.5. NADPH oxidase

NADPH oxidase is a membrane-bound enzyme complex that catalyzes the reduction of an electron from oxygen to superoxide through NADPH. NADPH oxidase, although it is a ROS producer, can be activated by ROS molecules. NADPH oxidase catalyzes the production of ROS from oxygen and NADPH in neutrophils, endothelial cells (vascular smooth muscle) and fibroblasts [31,56,91]. ROS produced by NADPH oxidase in moderate concentrations act as signaling molecules to regulate vascular tone [92]; however, excessive production of ROS leads to oxidative stress and vascular dysfunction [93]. Neutrophils and vascular NADPH oxidase are a key factor in oxidative stress induced by multiple inflammatory agents in the pathogenesis of preeclampsia [54,56].

It has been shown that the isoform of oxidized NADPH NOX 1 is overexpressed in syncytiotrophoblast of preeclamptic women's placentas. Two isoforms of NOX, NOX1 and NOX5 have been identified in cytotrophoblasts isolated from human placenta, which play an important role in both ROS generation and oxygen detection [94]. In preeclampsia, the activation of NADPH is triggered by the signaling of angiotensin II (Ang II) that leads to inflammation. Ang II stimulates NADPH oxidase through the AT1 AT1-AA receptor by causing the placenta to produce ROS, activating the nuclear factor kappa B (NF-κB) and subsequently triggering inflammation [95]. Other reports agree that in women with preeclampsia, the activity of NADPH oxidase increases [96,97] and, therefore, it represents an important source of $O2^{\bullet-}$ formation.

2.6. Obesity, oxidative stress and preeclampsia

Obesity has increased at an alarming rate and has been considered as a risk factor for preeclampsia, as well as for cardiovascular disease in adulthood. Obesity is defined as a body mass index (BMI) greater than or equal to 30 kg/m2. The World Health Organization estimates that by

2016, the prevalence of obese and overweight women (BMI ≥25 kg/m2) is 67.9% in the United States, 64.9% in Mexico, in United Kingdom 63.7%, 32.3% in China, 19.7% in India and 53.8% in South Africa, with a wide variation within each continent [98].

Obesity increases the overall risk of preeclampsia by approximately two or three times. The risk of preeclampsia increases progressively with increasing BMI, even within the normal range. It is important to note that not only the risk of late or mild preeclampsia increases, but also the risk of early and severe preeclampsia, which is associated with increased perinatal morbidity and mortality [99,100].

Metabolic factors related to obesity (lipids, insulin, glucose and leptin) increase the risk of developing preeclampsia by affecting several stages in pathogenesis: 1) placental dysfunction, altered migration of cytotrophoblasts and placental ischemia; 2) release of soluble placental factors in the maternal circulation induced by ischemia/hypoxia; and 3) maternal endothelial and vascular dysfunction [101].

The placenta is an essential organ formed during pregnancy that primarily transfers nutrients from the mother to the fetus; it also maintains its own development and function. The nutrients absorbed by the placenta are necessary for its own growth and development and to optimize fetal growth. Among the various nutrients, fatty acids, especially long chain polyunsaturated fatty acids (LCPUFA), including omega 3 and omega 6 fatty acids, are essential for placental development from the moment of implantation, as well as in the regulation of oxidative stress, angiogenesis and inflammation during pregnancy. During pregnancy, the placenta produces prooxidant and antioxidant substances and is able to reduce lipid peroxidation. However, certain structural and functional placental parameters are altered in pathological conditions, such as preeclampsia [102–104].

OS in the placenta has been widely related to unsaturated fatty acids; free radicals peroxidize the LCPUFA, causing an inflammatory response and cellular damage due to oxidative stress. An established method for measuring the end products of increased oxidative stress is to quantify the level of malondialdehyde (MDA), which is a final product of lipid peroxidation. Women with preeclampsia are more likely to have relative hypertriglyceridemia and hypercholesterolemia; an increase in the circulating concentrations of low density lipoproteins (LDL) and very low density lipoproteins (VLDL) with advance of gestational age, which is often replicated as a sharp increase in triglycerides and cholesterol, contribute to the increase in OS that leads to endothelial dysfunction and preeclampsia [105,106]. Total serum cholesterol levels in the first and second trimesters predict the onset of preeclampsia. In addition, hypertriglyceridemia increases sensitivity to develop endothelial dysfunction due to the reduced bioavailability of NO [107,108]. Leptin is an adipocin whose levels increase in relation to adiposity. It has been described that leptin reduces the proliferation of cytotrophoblasts, leptin levels increase in women with severe preeclampsia. Increased body fat is associated with elevated levels of circulating cytokines, infiltration of neutrophils in the blood vessels and increased blood pressure. Clinical studies have indicated a positive relationship between BMI and the activation of inflammatory pathways within the placenta. Fetuses of mothers with obesity show a higher production of proinflammatory adipocytokines, such as leptin, as well as increased insulin resistance and oxidative stress [101,109].

3. Conclusions

Pregnancy is a state of metabolic challenge that both the mother and the developing fetus must face, having the placenta as the main regulator in the response to oxidative stress, product of the fetoplacental energy demands. Alterations in placentation during the first trimester lead to the development of OS and dysfunction of the vascular endothelium that plays a key role for development in the occurrence of complications in pregnancy such as preeclampsia. Due to different scenarios that determine the prognosis of women who develop preeclampsia and for newborns, mostly premature babies, a more stringent criterion is needed in the evaluation of risk factors and obstetric monitoring of each particular case, that could offer prompt and appropriate treatment prior to the appearance of maternal complications, which would lead to suggest a different management, by means of a new vision of the effective antioxidant treatment in the risky pregnancy or, failing this, in the premature newborn immediately after birth, which can reduce maternal-perinatal morbidity and mortality.

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