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Oxidative Stress Markers in Pregnant Women with Preeclampsia

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Abstract Preeclampsia is a very important multisystem disorder to be specific to pregnancy, it is a disease mainly characterized by hypertension and proteinuria, but with unknown etiology that exposes the mother and the newborn to serious risks. One of the main factors involved in the pathophysiology of preeclampsia is oxidative stress and the rate of oxidative stress is measured by the ratio between the reactive oxygen species produced in the body called free radicals, and antioxidants produced by the body or absorbed through the diet. The excess of these free radicals have harmful effects, such as peroxidation of membrane lipids and aggression to tissue and membranes proteins as well as to membranes, enzymes, carbohydrates and DNA. Hypertensive disorders in pregnancy are a major cause of morbidity and maternal and fetal mortality. Preeclampsia is classified as a type of hypertensive complication that affects many pregnant women worldwide. The pregnancy and preeclampsia are conditions that increase susceptibility to oxidative stress, which in turn contributes to numerous complications, further aggravating the condition.

Keywords: *Oxidative Stress, Pregnancy, Preeclampsia, Biomarkers*

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1. Introduction

Preeclampsia is a multisystem disease of poorly understood etiology, it occurs in 2 to 8% of pregnancies and is a leading cause of neonatal and maternal morbidity and mortality [1], it is a specific clinical condition of pregnancy characterized by the onset of hypertension and proteinuria (300 mg or more of protein in urine of 24) after 20 weeks of gestation in pregnant women previously normotensive [2]. Since there is no cure for this disease during pregnancy, it has been more studied in order to increase the chance of discovering a biochemical marker for predicting the risk of preeclampsia [3].

The most frequent maternal complications of this syndrome are coagulopathy/HELLP syndrome of hemolysis, elevated liver enzymes and thrombocytopenia (10-20%), pulmonary edema (2-5%), renal failure (1-5%), premature separation of placentae (1-4%), brain edema, hemorrhagic shock, eclampsia (convulsions and/or coma), late cardiovascular morbidity and death. However, in the newborn, the most frequent complications are reduced amniotic fluid, fetal distress, intrauterine growth restriction (10-25%), prematurity (15-67%), low birth weight, future cardiovascular complications, may occur neurological damage by hypoxia and perinatal mortality, caused by low birth weight [1,4,5,6,7].

The main risk factors for preeclampsia are first pregnancy, previous preeclampsia, family history of preeclampsia/eclampsia and pathologies which develop increased trophoblastic mass as twin pregnancy, fetal hydrops and hydatidiform mole. For the prevention and treatment of preeclampsia the drug of choice is magnesium sulfate. However, women with blood pressure higher than or equal to 160 x 110 mmHg are treated with hypotensive agents, hydralazine and nifedipine are used as treatment of hypertensive crisis. When there is need for maintenance treatment, the drug of choice is methyldopa used orally [8].

The causes of preeclampsia have not been fully clarified, and there is currently no effective predictive test to identify women who are at risk for developing this disease, even with numerous research in this area [9].

2. Oxidative Stress

Oxidative stress is characterized by being a state of imbalance between the production of reactive oxygen species (ROS) and endogenous antioxidant [10], where there is an increase in ROS present in the body [11], being related to the etiology of a variety of diseases [10]. In the body, ROS are involved in energy production, regulation of cell growth, phagocytosis, in the synthesis of important biological substances and in intercellular signaling. When

in excess, however, there are adverse effects, such as lipid peroxidation and aggression to enzymes, DNA, carbohydrates and proteins and membranes of the tissues [12].

When there is error in the antioxidant system, and consequently an imbalance between production and removal of ROS/RNS, oxidative stress occurs, increasing the concentration of ROS/RNS and lipid peroxidation. These changes are able to cause damage to cellular structures of various tissues and organs, by changing vital functions and determining cell death [13,14].

Recent studies have implicated oxidative stress as one of the main factors involved in the pathophysiology of preeclampsia, and may influence the entire reproductive period of life of women [15]. Other studies support the hypothesis that oxidative stress may contribute to the etiology of the syndrome. Some evidence that they are in favor of this hypothesis are decreased antioxidant capacity, some abnormalities in proteins, lipids and DNA from the blood and the placenta [16]. During pregnancy oxidative stress may play a significant [17] role in influencing both the normal birth [18,19], as preterm labor [20,21].

Oxidants include reactive oxygen species, reactive nitrogen species, central sulfhydryl radicals and several others. Not all of these reactive species are radicals, i.e. molecules with one (or more) unpaired electrons, but in many cases the non-free radical reactive species will end up as radicals, damaging the biomolecules via oxidation [22]. Free radicals are atoms, ions or molecules containing an unpaired electron in their outer orbit. They are characterized by great instability and high reactivity and tend to turn the unpaired electron with other gifts in close to their training structures, behaving like receptors (oxidants) or donor (reducing) of electrons [23]. The danger of such kind of reaction is that the oxidation products formed are also radicals which in many cases are able to propagate the reaction, leading to extensive damage [22]. The free radicals can react with the major classes of biomolecules being the most susceptible lipids [23].

The gradual reduction of oxygen to water produces a variety of unstable intermediates, highly reactive and potentially toxic, among them is the O_2 (superoxide anion), H_2O_2 (hydrogen peroxide) and OH (hydroxyl radical). These forms of partially reduced oxygen are continuously generated in all aerobic cells as a result of oxidation processes, the main ROS in the body [24].

2.1. Oxidative Stress during Pregnancy

Although the etiology of preeclampsia is not defined, immunological, genetic factors and failure in placentation are currently the most accepted. Studies suggest that pregnant women with this condition have significantly higher levels of oxidative stress and minor amount of antioxidants (such as vitamin C and E) as compared to normal pregnant women, suggesting that preeclampsia is associated with an imbalance between the production of pro-oxidants and antioxidants, which facilitates lipid peroxidation of cell membranes causing injury to the vascular endothelium. Thus, oxidative stress contribute to endothelial dysfunction and for the pathophysiology of the disease [25,26].

Since the beginning of pregnancy, the human placenta influences maternal homeostasis, it is an environment rich in mitochondria and highly vascular, and it is exposed to high oxygen tension. Initially, the placenta has a hypoxic environment and as it develops and improves vascularization it evolves into an environment rich in oxygen, favoring the production of ROS [27,28]. During normal pregnancy there is a slight increase in oxidative stress, even in the presence of antioxidant systems since the beginning of pregnancy, such as catalase, GPX, vitamin C, glutathione, among others [29,30]. In fact, during normal pregnancy which occurs is a transient increase in the production of ROS, which is partially offset by the induction of antioxidant systems [31,32]. Thus, pregnancy is a condition that increases the susceptibility to oxidative stress.

The transformed trophoblastic invasion of the uterine hemodynamic system a low-flow and high resistance in a high and low flow resistance. Partial or total changes in trophoblastic invasion appear to predispose to complications such as preeclampsia and intrauterine growth [33]. In preeclampsia, due to failure of trophoblastic invasion, an inadequate blood perfusion accurs leading to areas of ischemia and reperfusion which increases the generation of ROS and cause activation of neutrophils and leukocytes. ERO is the most common Superoxide (O_2^-), generated by NADPH oxidase in cells, xanthine oxidase enzymes and the electron transport chain of mitochondria. Neutrophils isolated from women with preeclampsia synthesize more superoxide than normal pregnant women, and this is mediated by NADPH oxidase [34].

After birth, the level of antioxidants and ROS, RNS and other oxidative compounds, returning to normal levels [32,35]. The type of delivery may also influence the state of oxidative stress, studies show that normal vaginal delivery is associated with a higher level of oxidative stress compared with cesarean delivery [36].

In the newborn, preeclampsia, as well as being associated with prematurity, low birth weight and the restriction of intrauterine growth, can cause imbalance in the oxidant/antioxidant, causing the development of neonatal diseases associated with oxidative stress, especially in preterm infants, as respiratory distress syndrome, bronchopulmonary dysplasia, periintraventricular hemorrhage, retinopathy of prematurity and necrotizing enterocolitis [37,38,39].

Some treatments with antioxidants have been conducted in mice to verify the effectiveness of supplementation with antioxidants, quercetin and glutathione. These studies have shown a reduction in the mortality rate in animals, there was also a decrease in proteinuria and plasma levels of lipid peroxidation back to normal [40]. Thus, in attempting to treat or prevent the pathology of pre-eclampsia, there have been attempted to reduce oxidative stress in women who have an increased risk of developing pathology.

2.2. Biomarkers of Oxidative Stress

In the pathophysiology of preeclampsia, the main by-products of oxidative stress are derived from lipid peroxidation represented by peroxilipids [41]. Lipid peroxidation generates a well-known product is the

malondialdehyde (MDA) [42,43], it is the end product of non-enzymatic degradation of polyunsaturated fatty acids [44]. The test MDA using the TBARS assay, it is among the most commonly used markers for assessing damage by lipid oxidation. This test identifies lipid oxidation products, amino acids, bile pigments and sugars that can cause interferences due to interfering chromogens which are formed. From this, it is more appropriate to use the term thiobarbituric acid (TBARS) [41].

Studies have shown that exposure to ROS cell membranes predisposes the occurrence of lipid peroxidation, thus contributing to cell damage for promoting change in the physical properties and structural organization of membrane components [45,46]. Lipid peroxidation ROS attack the polyunsaturated fatty acids of the phospholipids of cell membranes, cell disintegration occurs and thus there is the entry of such these species within the cell [23]. Some studies have reported a progressive increase in TBARS levels during pregnancy and can be used to predict the occurrence of preeclampsia [47,48]. The lipid oxidation due to preeclampsia may explain the similar morphological changes found between preeclampsia and acute atherosis [49], and the association with high cardiovascular risk, atheroma formation, and coronary artery disease, as repeatedly mentioned by many authors [50].

Another oxidative stress marker are the thiol groups that are biological markers of protection of proteins against oxidative stress, being susceptible to oxidative damage. These compounds, and other redox sensitive molecules, play a significant role in the cell, thereby minimizing the deleterious effect of oxygen activation processes. Essentially all plasma protein SH groups are attached and such as albumin is the most abundant protein in the plasma, they partly lose their extracellular antioxidant power. Therefore, the decrease found in thiol can also be seen very early protein product oxidation [51].

The presence of proteinuria in pregnant women with preeclampsia reflects the installation of relevant changes in renal function, resulting from glomerular lesions, among which the most common is the glomeruloendoteliose. Usually, proteinuria is detected on average three to four weeks before changes in the fetal development and/or worsening of the maternal clinical status [52]. Thus, the dosage of the thiol groups may be even lower in pregnant women with this condition.

Antioxidants produced or absorbed by the body in fighting the diet excess of free radicals [53]. Enzymes such as catalase (CAT) and superoxide dismutase (SOD), along with the dietary antioxidants such as vitamin C and α-tocopherol are the main antioxidant defense of the organism against oxidative damage [23]. According to the classic definition, "antioxidants" are molecules which, when present at low concentrations compared with the oxidizable substrate must protect, prevent or reduce its oxidation or regenerate it [54]. In addition to enzymes and compounds absorbed through the diet, some proteins present in the body also act as antioxidants systems, such as proteins that bind to metals (ferritin and transferrin) and which bind to the heme of hemoglobin (haptoglobin) [55]. Since bilirubin, from the heme metabolism, is a very potent antioxidant against lipid peroxidation [56].

Some studies suggest that in patients with preeclampsia, ascorbate can be used to compensate for changes in cells mediated by free radicals [57-61] and other studies suggest that vitamin C supplementation can prevent preeclampsia in women who have a increased risk to develop the disease [62,63]. However, some recent studies have shown an increased risk of low birth weight of children born in the group of pregnant women who received this supplementation [64,65].

Vitamin C is present in aqueous compartments, such as the cytosol, plasma and other body fluids, it is able to trap ROS found at these sites and it works as a first line defense mechanism against free radicals [66]. Vitamin C is derived exclusively from the diet and is vital for all human beings who cannot synthesize it. This vitamin has a great role as an antioxidant as well as being capable of reducing ROS and RNS, also being able to regenerate vitamin E [67].

The main antioxidant enzymes that are present in the placenta, such as SOD, catalase (CAT), GPx, gluitationa reductase, glutathione S-transferase and glucose-6-phosphate dehydrogenase, they seem to have their activity decreased in women with preeclampsia [68]. SOD, which comprises three isoforms: SOD-copper-zinc (mainly present in the cytosol), Mn-SOD (localized primarily in the mitochondria) and extracellular SOD is a major defense system vascular cell [69]. This enzyme acts as an antioxidant because it catalyzes the dismutation of $\cdot O_2^-$ anion as H_2O_2 and O_2, in the presence of hydrogen (H^+). Under physiological conditions, the concentration $\bullet O_2^-$ is low and SOD concentration is high, thus favoring disproportionation catalyzed by SOD [70,71]. With the rapid cellular response to damage due to oxidative stress, there is an increase in defensive SOD expression, it works in conjunction with other enzymes to remove excess of H_2O_2, among enzymes that assist in this removal is catalase and glutathione peroxidase [72].

The catalase is also very effective in high levels of oxidative stress, it is a plasma hemoprotein located in peroxisomes and cytosol, exerts its antioxidant activity to catalyze the reduction of H_2O_2 to H_2O and O_2 [13]. When H_2O_2 is not neutralized it interacts with iron cations (or copper), to give the hydroxyl ion and the free hydroxyl radical. So in addition to his role as ROS, when the H_2O_2 is in excess causes oxidation of hemoglobin, causing a decrease in oxygen concentration in the cell, may be involved in the development of various diseases [73].

Another enzyme which seems to be altered in women with preeclampsia is sulfidrilic enzyme delta-aminolevulinate dehydratase (ALA-D-δ) that is part of the heme biosynthetic pathway [74], is essential for aerobic organisms [75] and in pro-oxidant conditions can be inhibited [74]. This inhibition, besides the insufficient production of heme [76], may result in the accumulation of 5-aminolevulinic acid (ALA) which is related to the overproduction of reactive oxygen species [77]. The δ-ALA-D can be inhibited by substances that oxidize -SH groups or competing with zinc [78,79,80,81]. The decrease in activity of this enzyme also implies high circulating levels of free radicals H_2O_2 and O_2, and these, along with the ALA can be a significant factor in endothelial dysfunction commonly seen in the condition of preeclampsia. Therefore, this enzyme can be suggested as an indirect marker of oxidative stress because the modulation of the activity of this enzyme contributes

significantly to the global burden of oxidative stress [82,83].

In addition to these cited markers, a number of other markers of oxidative stress may be altered in the pathophysiology of preeclampsia, so it is of great relevance to studies to evaluate these markers.

3. Conclusion

In preeclampsia there is a state of imbalance, where free radicals are high, without a compensatory increase of antioxidant. Deleterious effects may be produced due to multiple independent pathways that are activated, they contribute to the induction or the propagation of oxidative stress. Although the clinical and biochemical pattern of preeclampsia disappear within a month after birth, the oxidative stress markers do not return to normal quickly. These indicators take four months after the birth to get back to normal, showing that oxidative stress markers are very reliable and sensitive indices to highlight these changes in women with this disease [84].

Still, there are many gaps to be unveiled on the pathophysiology of preeclampsia where the immune activation, genetic inheritance and oxidative stress interact in the aggravation of the injury endothelial process. Some therapeutic strategies involving the reduction of oxidative stress and modulation of the immune response may be part of the management of patients with this pathology. However, currently there is not much to be done other than to identify pregnant women who have a high risk for developing preeclampsia, because there is no specific treatment after clinical worsening of the patient, increasing the risk of morbidity and mortality and mother/or the fetus.

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