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Role of oxidative stress in the pathogenesis of preeclampsia

Imran A. Siddiqui · Anila Jaleel · Waleed Tamimi · Hanan M. F. Al Kadri

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Abstract Hypertensive disorders of pregnancy are associated with an increased risk of maternal and fetal morbidity and mortality. The cause and the pathogenesis of the pregnancy-induced syndrome, preeclampsia, is still poorly understood. Published evidence of altered biomarkers for the endothelial dysfunction suggests that the initiating event in preeclampsia is the reduced placental perfusion, which leads to widespread dysfunction of the maternal vascular endothelium. This review focuses on the role of free radicals in generating the oxidative stress taking antioxidants into consideration which tend to overcome it as well as the role of placenta in preeclamptic pregnancy.

Keywords Oxidative stress · Endothelial dysfunction · Preeclampsia · Antioxidants

I. A. Siddiqui (✉)
College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, MC: 3127, PO Box 22490, Riyadh 11426, Kingdom of Saudi Arabia
e-mail: siddiquiimra@gmail.com

A. Jaleel
Department of Biochemistry, Ziauddin Medical University, Karachi, Pakistan

W. Tamimi
Department of Pathology and Laboratory Science, King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia

H. M. F. Al Kadri
Department of OB/GYN, King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia

Introduction

Preeclampsia is a multisystem and multifactorial disease that affects both the mother and the fetus by vascular dysfunction and by intrauterine growth restriction, respectively. It is estimated to affect 5–8% of all pregnancies, being the leading cause of death in developing countries and a major contributor to maternal and perinatal morbidity [1]. Preeclampsia is diagnosed if the systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, accompanied by proteinuria with at least 300 mg protein in a 24 h urine collection [or ≥1+ dipstick (30 mg/dL) in a single urine sample] first detected after 20 weeks of gestation [2]. In the past, other components such as edema have been included in the definition of preeclampsia but it can be a feature of normal pregnancy; moreover, these components do not define a group at risk of poor outcome [3]. Women with mild preeclampsia generally have no symptoms. However, women with severe preeclampsia (usually BP ≥ 160/110 mmHg and/or proteinuria ≥ 2–5 g/24 h) may have signs and symptoms such as renal insufficiency (reduced urinary volume, raised serum creatinine), liver disease (upper abdominal pain, elevated liver enzymes), neurological disturbances (headache, visual disturbances, exaggerated tendon reflexes, convulsions (eclampsia)), and haematological disturbances (thrombocytopenia, disseminated intravascular coagulation, hemolysis) [2]. Preeclampsia is characterized by vasospasm, abnormal placentation and reduced placental perfusion. The major cause of fetal compromise is uteroplacental perfusion. The only cure is delivery of the baby [4]. When preeclampsia develops, the mother and her baby are monitored carefully. There are medications and treatments that may prolong the pregnancy, which can increase the baby's chances of health and survival. Unfortunately,

once the course of preeclampsia has begun, the health of the mother must be constantly weighed against the health of the baby. In some cases, the baby must be delivered immediately, regardless of gestational age, to save the mother's and/or baby's lives [5]. A large portion of the perinatal mortality is therefore due to iatrogenic prematurity, up to 15% of preterm births are a result of preeclampsia [6].

Maternal endothelial dysfunction is widespread and explains all the clinical signs of the disease [7]. The mechanisms involved in the endothelial dysfunction are poorly understood. Abnormal placentation is clearly involved in the development of both preeclampsia and fetal intrauterine growth restriction. Some studies support notions of inadequate blood supply to the placenta making it release particular hormones or chemical agents that leads to damage of the endothelium (lining of blood vessels), alterations in metabolism, inflammation, and other possible reactions in mothers predisposed to the condition [8]. In the past several years, evidences have been accumulating that there is a second important biochemical imbalance in preeclampsia; that is, women with preeclampsia have an increased oxidative stress and lipid peroxidation and at the same time have a deficiency in several important antioxidants [9]. This review briefly describes the free radicals, antioxidants, oxidative stress and the role of placenta in preeclampsia.

Free radicals and oxidative stress

Free radicals are highly reactive molecules that have one or more unpaired electrons. Reactive oxygen species (ROS) such as super oxide, hydrogen peroxide, and hydroxyl radical are associated with cell damage. ROSs forms as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling [10]. The double bonds of polyunsaturated fatty acids (PUFA) are highly susceptible to oxidation by oxygen free radicals. Polyunsaturated fatty acids are found in abundance in cell membranes and circulating lipoproteins, hence these structures are highly susceptible to oxidation and the process of lipid peroxidation. Reactive oxygen species arising from the various sources [11] such as mitochondria, through the electron transport chain and cytochrome P450 are a major source in aerobic cells. Oxidative enzymes, stimulated neutrophils through the activity of NADPH oxidase, oxidation of catecholamine and metabolism of arachidonic acid by both the cyclooxigenase and lipoxigenase pathways generate oxygen radicals [12]. Superoxide (O_2^-) and hydrogen peroxide (H_2O_2) generated from various routes react directly with each other in the presence of free transition metals, in particular, iron, and generate the extremely reactive hydroxyl radical (·OH) by Haber–Weiss and Fenton reaction ($O_2^- + H_2O_2 \rightarrow \cdot OH + HO^- + O_2$) [13]. Similarly, lipid peroxides and hydrogen peroxide, in the presence of the transition metals initiate the chain reaction of lipid peroxidation that continues until it is interrupted by an antioxidant [14].

Antioxidants

Antioxidants are molecules capable of slowing or preventing the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals which initiate chain reactions that damage cells. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves [15]. Antioxidants are derived either from endogenous synthesis such as superoxide dismutase, catalase, glutathione peroxidase or from diet (vitamin A, vitamin C, vitamin E) [16]. The major plasma antioxidants are transferrin, lactoferrin, ceruloplasmin, albumin, uric acid and haptoglobins which chelate transition metal ions such as iron and copper and prevent them from catalyzing the production of free radicals in the cell [17]. Vitamin C scavenges the water soluble radicals while vitamin E scavenges the lipid soluble free radicals. Increased oxidative stress and lipid peroxidation can result in decrease in the levels of these vitamin antioxidants [18]. The intracellular antioxidant enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) serve as primary line of defense in destroying free radicals. SOD first reduces (adds an electron to) the radical superoxide (O_2^-) to form hydrogen peroxide (H_2O_2) and oxygen (O_2). Catalase and GPx then work simultaneously with the protein glutathione to reduce hydrogen peroxide and ultimately produce water (H_2O) [19]. Vitamin E acts as an antioxidant in the plasma and, being a lipid soluble vitamin, becomes a constituent of the cell membrane and the membranes of intracellular organelles and hence prevents the lipid peroxidation of the plasma [20].

Oxidative stress in pregnancy

Normal pregnant women exhibit an increase in lipid peroxidation and oxidative stress compared with non-pregnant women [21]. Pregnancy is characterized by dynamic changes in multiple body systems resulting in increased basal oxygen and energy consumption in different organs including the fetoplacental unit. Initially the placenta has a hypoxic environment but with maturity, its vascularization develops which changes it to an oxygen rich environment [22]. The placenta is rich in mitochondria, highly vascular, consumes about 1% of the basal metabolic rate of the pregnant woman and is exposed to high maternal oxygen

partial pressure, therefore resulting in increased production of reactive oxygen species. It increases the liberation of free iron from iron sulfur clusters which, in reactive form, produce hydroxyl radicals (·OH^-) mainly through catalyzing Haber–Weiss reaction [23].

Nitric oxide (NO) is also locally produced by the placenta and together with other reactive nitrogen species contributes to potential oxidative stress in the presence of transition metals [24]. Placenta is also rich in macrophages favoring the local placental production of free radicals like reactive chlorine species (RClS) by autocatalysis in the presence of iron [25]. Reduced glutathione in erythrocyte lysate which can be oxidized and produce reactive oxygen species again in the presence of iron, is elevated in pregnancy [26]. Superoxide dismutase (SOD) activity in erythrocytes and plasma thiols levels were found to be lower and ceruloplasmin levels were found to be higher in pregnant than in non-pregnant women, suggesting increased oxidative stress during pregnancy [27].

Defense mechanisms against free radical damage are also enhanced as pregnancy progresses. The body on account of susceptibility to oxidative insult is naturally provided with an efficient antioxidant system. Placental homogenates and syncytiotrophoblastic brush border preparations from interrupted pregnancies, early, at midgestation and at term, show progressive increments in free radical scavengers such as bilirubin and glutathione as well as in the specific activities of SOD, catalase and glutathione peroxidase and reductase [28]. Glutathione peroxidase in erythrocytes and platelets and extracellular SOD activity have also been found to increase progressively throughout gestation up to the third trimester, possibly as a response to increased presence of $O_2^{\cdot-}$ [29]. In normal pregnancy, the ratio of prostacyclin to thromboxane favors prostacyclin, suggesting an effective defense system against oxidative stress [30].

The role of vitamins A, C and E in preventing free radical damage is well known and their nutritional adequacy is important in pregnancy. The placenta efficiently absorbs vitamin C so that when maternal plasma ascorbic acid concentration is low, it is absorbed by active mechanisms. At higher plasma ascorbic acid concentrations it enters the placenta by passive diffusion [31]. Generally, α-tocopherol contents decrease in the total placenta and in the syncytiotrophoblastic brush border membrane as pregnancy progresses but vitamin E ingestion can elevate it [32]. However, to date there is no strong evidence in support of routine antioxidant supplementation during pregnancy to reduce the risk of preeclampsia [33].

Oxidative stress in preeclampsia

Several studies relate the development of preeclampsia with the inadequate invasion of the trophoblast and uterine artery remodeling due to the abnormal regulation of cell–cell and cell–matrix interaction [34, 35]. This results in reduced uteroplacental perfusion and placental ischemia which might release products into the maternal circulation, responsible for initiating the pathophysiological changes of preeclampsia [36].

In contrast to normal pregnancy, preeclampsia is characterized by increased oxidative stress and decreased antioxidants [37] (Fig. 1). In preeclamptic women, maternal circulating levels, placental tissue levels and production rate of lipid peroxides are increased and several antioxidants are markedly decreased [18, 38]. In the maternal circulation, the levels of vitamin A, C, E, glutathione, iron binding capacity, and superoxide dismutase are altered [39]. Rosta et al. [40] suggested the role of SOD3 single nucleotide gene polymorphism in the increased oxidative stress in preeclampsia. A significant decrease in tissue levels of vitamin E, and in the activities of superoxide dismutase and glutathione peroxidase are found in the placenta of these women [41]. Due to the deficiency of the superoxide dismutase activity, the concentration of superoxide anion concentration is increased, which in conjunction with increased concentration of iron would result in greater oxidative stress [42]. In the presence of deficiency of superoxide dismutase activity, nitric oxide (NO) reacts with superoxide to form peroxynitrite ($ONOO^-$) which is a strong oxidizing agent capable of initiating lipid peroxidation. Since NO is a potent vasodilator, at times when SOD is deficient, not only the vasodilating action of nitric oxide is impaired but also a strong oxidizing agent is produced [43]. Another source of oxidative stress in

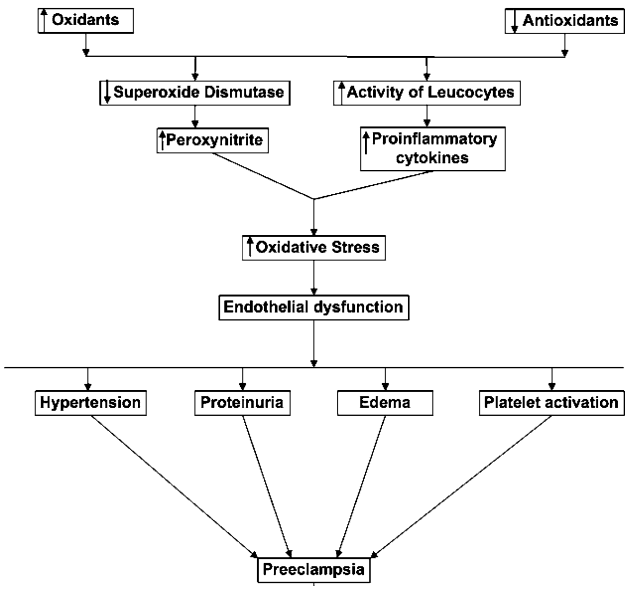

Fig. 1 Suggested role of oxidative stress in the pathophysiology of preeclampsia

preeclamptic women is the activation of leukocytes in their circulation. It has been reported that in preeclampsia, maternal circulating neutrophils and monocytes are activated, which generate superoxides (O_2) by the activity of NADPH oxidase and hence cause oxidative stress. Activated neutrophils also produce cytokines such as tumor necrosis factor (TNF-α), interleukin-6 (IL-6) and vascular adhesion molecule VCAM-1, indicating leukocyte-endothelial attachment and activation [44]. This activation of endothelial cells produces local damage and dysfunction of the cells leading to lipid peroxidation of the cell membrane. Many markers of endothelial dysfunction have been reported in women who develop preeclampsia, suggesting that preeclampsia is an endothelial cell disorder [45]. An imbalance of anticoagulant and procoagulant forces is found in preeclampsia as increased levels of proteins of the coagulation cascade have been reported in these women [46]. Circulating levels of fibronectin are significantly increased in women who develop preeclampsia as early as 20 weeks of pregnancy [47]. Plasma thrombomodulin, an anticoagulation factor, is also significantly elevated in women with preeclampsia, with elevations detected as early as 24 weeks into the pregnancy [48]. Biomarkers may also reflect severity of the disorder as circulating levels of fibronectin and thrombomodulin increase relative to severity of the disease. Von Willebrand factor, another coagulation cascade factor, is also elevated in women with preeclampsia [49]. Platelets also appear to play an important role in the etiology of preeclampsia. Enhanced platelet activation as determined by whole blood flow cytometry, and increased levels of platelet endothelial cell adhesion molecule-1 (PCAM-1) also occur in preeclamptic women [50]. Plasma levels of other adhesion cell molecules such as vascular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin are found to be elevated [51, 52]. Plasma levels of ICAM-1 and VCAM-1 have been reported to be significantly elevated at 3–15 weeks before onset of clinical manifestations. Elevations in ICAM-1 were evidenced at 18 weeks of gestation, thus suggesting that the markers of endothelial dysfunction may serve as predictors of preeclampsia during pregnancy [53, 54]. Recently, Molvarec et al. [55] reported the raised levels of serum hock protein 70, the acute phase reactant in preeclampsia, suggesting the role of oxidative stress in the disease.

Conclusion

The available literature reveals that oxidative stress is actually the presence of the reactive oxygen species in excess of the buffering capacity of the available antioxidants, influencing the normal pregnancy. Preeclampsia is characterized by increased oxidative stress due to the imbalance between lipid peroxidation and antioxidant defense mechanisms, leading to endothelial dysfunction and free radical mediated cell injury. Other maternal factors including activated neutrophils and imbalance between anticoagulants and procoagulants aggravate the oxidative stress and endothelial dysfunction. A comprehensive understanding and the detailed knowledge of the pathogenesis of the preeclampsia will enable us to identify the responsible contributing biomolecules for this disease. Measurement of these contributing biomolecules can help us in predicting the disease earlier. It is hoped that we can identify the biomarkers of preeclampsia with high predictive, preventive, and prognostic value and incorporate with current clinical practice to improve the care for pregnant women.

Conflict of interest statement None.

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