Fundamental Role of Oxidative Stress in the Pathophysiology of Preeclampsia: A Review

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Abstract Oxidative stress and systemic inflammatory response can emerge at the same time, exacerbate the effect of the other, and cause irreversible damage. In addition to the fundamental role of oxidative stress in the pathophysiology of preeclampsia, molecular evidence of high levels of endoplasmic reticulum (ER) stress is also found. Searches were conducted by two independent researchers in international (PubMed, Web of science, Scopus and Google scholar) and national (SID, Magiran) databases for related studies from the inception of the databases to September 2017 (without time limitation) in English and Persian languages. To ensure literature saturation, the reference lists of included studies or relevant reviews identified through the search were scanned. The specific search strategies were created by a Health Sciences Librarian with expertise in systematic review search using the MESH terms and free terms according to the PRESS standard. The most important lesion of the pairs in preeclampsia is acute atherosclerosis of decidua arteries. This lesion is partly due to the abnormal alignment between the spiral arteries and the cytotrophoblast that causes insufficient ventilation. This can lead to inadequate blood supply, which causes oligohydramnios, intrauterine growth retardation, pairing, fetal distress, and ultimately fetal death.

Keywords oxidative stress, pathophysiology, preeclampsia

Introduction
Oxidative stress and systemic inflammatory response can emerge at the same time, exacerbate the effect of the other, and cause irreversible damage. In addition to the fundamental role of oxidative stress in the pathophysiology of preeclampsia, molecular evidence of high levels of endoplasmic reticulum (ER) stress is also found [1]. ER is the site of synthesis and changes after transfusion of proteins and the center of coordination of various pathways of metabolism, proliferation and cell death. Disruption of ER function is known as ER stress [2]. During the last decade, there has been reported a link between endoplasmic stress and oxidative stress, and it can be said that oxidative stress and ER stress are both effective in the pathophysiology of preeclampsia. ER stresses, such as oxidative stress, trigger the prognostic response [3].

In the pathology of preeclampsia, many putative factors, such as pro-inflammatory cytokines and angiogenic factors, have turned out to be implicated, but so far a specific factor that can be observed for all cases of preeclampsia has not been identified. This, most of all, indicates that this syndrome can be initiated by various factors and the interaction of various cellular and molecular structures [4].
Methods

Search Strategy

Searches were conducted by two independent researchers in international (PubMed, Web of science, Scopus and Google scholar) and national (SID, Magiran) databases for related studies from the inception of the databases to September 2017 (without time limitation) in English and Persian languages. To ensure literature saturation, the reference lists of included studies or relevant reviews identified through the search were scanned. The specific search strategies were created by a Health Sciences Librarian with expertise in systematic review search using the MESH terms and free terms according to the PRESS standard. After the MEDLINE strategy was finalized, it was adapted to search in other databases. Accordingly, PROSPERO was searched for ongoing or recently completed systematic reviews. The key words used in the search strategy were “oxidative stress, pathophysiology, preeclampsia” and Iran which were combined with Boolean operators including AND, OR, and NOT.

Study Selection

Results of the Literature review were exported to Endnote. Prior to the formal screening process, a calibration exercise was undertaken to pilot and refine the screening. Formal screening process of titles and abstracts were conducted by two researchers according to the eligibility criteria, and consensus method was used for solving controversies among the two researchers. The full text was obtained for all titles that met the inclusion criteria. Additional information was retrieved from the study authors in order to resolve queries regarding the eligibility criteria. The reasons for the exclusion criteria were recorded. Neither of the review authors was blinded to the journal titles, the study authors or institutions.

![Diagram](image)

*Figure 1: Factors involved in the occurrence of preeclampsia*
Pathophysiology of preeclampsia

Hypertension changes seen in preeclampsia are associated with severe vascular contraction with segmental spasm, which occurs especially in the hepatocytes and is thought to be due to increased vascular responsiveness [5]. The mechanism responsible for increasing vascular reactivity is believed to occur in the natural interactions between vasodilator (prostacyclin, nitric oxide) and vasoconstrictor (thromboxane A2, endothelin). These changes lead to an increase in arterial blood pressure (afterload). Another vascular symptom of preeclampsia is blood condensation [6]. Patients with preeclampsia suffer blood congestion. Patients with preeclampsia have fewer intruterine volumes and lower tolerance for their loss of blood during pregnancy. Endothelial damage appears to stimulate intravascular fluid leakage and protein interstitial space and reduce intravascular volume. The heart of a healthy woman with preeclampsia is normal in terms of performance and contractility [7].

In preeclampsia, several coagulation disorders can occur. The most common abnormalities in preeclampsia is thrombocytopenia (a platelet count of less than 100,000 / mm³). Pathophysiological mechanism is likely to damage or activate endothelial vascular and high levels of thromboxane A2 [8]. Micro-angiopathic anomalies (as seen in HELLP syndrome) can be detected by observing schistocytes in the development of peripheral blood and increased levels of lactate dehydrogenase (LDH). Interpreting the baseline hematocrit in a patient with preeclampsia may be difficult. The low hematocrit may be due to hemolysis, and hematocrit, which is falsely high, can be due to blood condensation [9].

The vasoconstriction reduces blood flow to the kidneys and consequently reduces the amount of glomerular filtration (GFR) in preeclampsia. In normal pregnancy, GFR levels increase by up to 50% compared to pre-pregnancy. Similarly, serum creatinine levels in patients with preeclampsia are rarely higher than normal pregnancy levels (0.8 mg / dl) [10]. Precise monitoring of urine output is necessary in patients with preeclampsia, as oliguria may occur due to renal failure (which is a urine volume less than 500 cc in 24 hours). In rare cases, severe renal failure may lead to acute tubular necrosis. Renal pelvic lesions in preeclampsia are called glomerular capillary endothelium, which is the swelling of mesangial and endothelial cells of glomerular capillaries [11].

Liver damage associated with preeclampsia is caused by a mild elevation of liver enzymes to hepatocellular hematomas and liver rupture. Recent injuries are commonly associated with HELLP syndrome. Approximately 20% of maternal mortality in preeclampsia is related to liver complications. Liver pathology lesions seen in autopsy include peritonneal hemorrhages, hepatocellular necrosis, ischemic lesions of intracellular fatty changes, and fibrin sedimentation [12].

Eclampsia seizure is probably the most worrying complication of preeclampsia in the central nervous system (CNS) and is still one of the main causes of maternal mortality in the Third World. The exact etiology of eclampsia is unknown, but scientists believe that it might occur due to coagulation disorder, fibrin deposition and vascular spasm occur [13]. The most common finding in the brain is edema, which is probably due to vascular dysfunction. Radiological studies may show evidence of cerebral edema and hemorrhagic lesions, especially in the posterior cerebral hemispheres that can account for visual impairment associated with preeclampsia [14]. Other CNS abnormalities include headaches and various types of visual disorders such as night blindness, blurred vision, and rarely temporary blindness.

The most important lesion of the pairs in preeclampsia is acute atherosclerosis of decidua arteries. This lesion is partly due to the abnormal alignment between the spiral arteries and the cytotrophoblast that causes insufficient ventilation. This can lead to inadequate blood supply, which causes oligohydramnios, intrauterine growth retardation, pairing, fetal distress, and ultimately fetal death [15].

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