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Mechanisms involved in the incidence of preeclampsia: A review

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ABSTRACT

In 1916, preeclampsia syndrome was officially called a *disease*, and now, after nearly a century, the exact cause of preeclampsia syndrome has not yet been determined. Several assumptions have been made in this regard, including the effects of immunological factors, coagulation disorders, nutritional factors, and increased production of reactive oxygen species (ROS).

Method: 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.

Discussion: all pregnancies are associated with a systemic maternal inflammatory response, in which peripheral granulocytes, monocytes and lymphocytes increase during the third trimester of pregnancy. This condition intensifies in preeclampsia pregnancies, and some pro-inflammatory factors in the maternal circulation and cytokines that activate the endothelial cells increase

KEY WORDS: preeclampsia, preeclampsia syndrome, Review

INTRODUCTION:

In 1916, preeclampsia syndrome was officially called a *disease*, and now, after nearly a century, the exact cause of preeclampsia syndrome has not yet been determined. Several assumptions have been made in this regard, including the effects of immunological factors, coagulation disorders, nutritional factors, and increased production of reactive oxygen species (ROS) (1). The latter case has recently been considered by scientists. Recent studies confirm that the pair plays a central role in the pathogenesis of preeclampsia and the placenta hypoxia can be one of the causes of this disease. During the early stages of normal pregnancy, trophoblast cells attack the spleen arteries and y replace the regenerative endothelial cellsprogressively (2). By the end of the second trimester of pregnancy, these veins lose their muscular and elastic components. In fact, the layer of myometrium, which contains a lot of contractile proteins, disappears, and instead, the fibrinoid layer is deposited by the trophoblast cells (3). As a result, spiral arteries turn into loose and wrinkled tubes with a diameter of at least 4 times the pre-pregnancy rate. This makes it possible for a fast-growing, low-fetal blood-thirst for a fetus to grow. In addition, the loss of regenerative wall elements makes these arteries unresponsive to vascular activation stimuli (4). This regurgitation transformation process involves all 100-150 spiral arteries present in the placenta. However, studies done on the uterus of preeclampsia patients suggest that trophoblast cells do not attack spiral arteries efficiently. As a result, the deformation of the spiral arteries remains incomplete, which causes decreased rate of placental infusion in these individuals compared to normal pregnancies (5).

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 identifed through the search were scanned. The specifc 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

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the MEDLINE strategy was finalized, it was adapted to search in other databases. Accordingly, PROSPERO was searched for ongoing or recently related completed systematic reviews. The key words used in the search strategy were "preeclampsia, preeclampsia syndrome" 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.

Discussion:

This assessment is confirmed by the Doppler ultrasound of blood flow in the uterine vessels. In a series of similar studies, the amount of blood entering the uterus or the placenta was reduced by surgery in animals (6). The results of these studies indicated elevated blood pressure, similar to that seen in humans. These studies indicate that preeclampsia results from a chronic hypoxia condition(7).

Although hypoxia appears to be one of the pathologic factors of preeclampsia, several reports have rejected such a claim. reported that the amount of metabolized energy in the normal condition and in the presence of the disease was similar in measuring peripheral metabolism in preeclampsia conditions (8). Also, some studies have reported cases of preeclampsia in which spiral arteries were in a healthy, non-injured pair. It should be noted that similar reggae pathology may also be observed in other abnormalities of pregnancy, such as preterm labor (9). This evidence suggests that the pure oxygen concentration in the capillary space does not play a decisive role in the pathogenesis of preeclampsia and another hypothesis should be followed to provide authentic, valid findings in this regard.

Another hypothesis about the mechanism of preeclampsia is the effect of the damage of oxygen deficiency – hypoxia reoxygenation- in the disease (10). It is worth noting that there is also a basic condition of drop in blood flow in all natural pregnancies. But this situation intensifies in preeclampsia patients with spiral vein problems, because the remaining muscle components of the uterine tissue cause some contractions of regurgitation to occur on their own, and the environment of the uterus and the placenta change in relative to the stimuli of External regurgitation (exogenous) and internal (endogenous) excitability (11). Stopping blood flow due to regurgitation contraction with the rest of the vessel is neutralized and this results in the production of more reactive oxygen radicals. In case of lack of oxygen, implying the insufficiency of oxygen for the acceptance of electron-chain, these electrons accumulate and when the oxygen concentration increases suddenly and severely during re-oxygenation, the electrons are transported unorganized into oxygen and reactive oxygen-producing radicals. This route is one of the sources of ROS production in this situation (12). To support this hypothesis, a test was designed to cultivate the pair under conditions of lack of oxygen - re-oxygenation. It was found that the amount of ROS produced in endothelial and trophoblast cells is much higher than hypoxia alone (13).

The ROS produced by multiple reactions generates oxidative stress conditions and can affect molecules and cellular messaging pathways. A bunch of these molecules are proteins that are prone to changes after a variety of transcriptions. It has been determined that these changes, in particular changes in redox (oxidation and regeneration) of proteins, can function in vivo (14). In case of preeclampsia, among various proteins, the proteins present in the renin-angiotensin system (RAS) are the likely purposes of these changes, because this system plays a major role in regulating and maintaining the internal stability of blood pressure. In RAS, angiotensinogen (AGT) by is broken down into angiotensin I the enzyme Renin. This angiotensin form is called angiotensin converting enzyme at the level of the endothelial cells of the regiard, which converts it into angiotensin II. Angiotensin II is a potent vasoconstrictor that increases blood pressure (15).

Angiotensinogen has two forms of oxidation and regeneration. The results of Zhou et al.'s study showed that the formation of a di-sulfide bridge in

the form of an AGT oxide causes structural changes in the molecule, which connects it to Renin and, as a result, facilitates the release of angiotensin I. The study also found that the AGT ratio of reduction to AGT oxide, which is normally 40 to 60, is altered in preeclampsia patients, which reduces AGT levels and stimulates the more active form of AGT oxide. This may be one of the reasons for hypertension in preeclampsia patients. What is certain is that oxidative stress releases many factors in the maternal circulation, each of which can contribute to the pathogenesis of preeclampsia and increased blood pressure (16).

These factors stimulate inflammatory response and activate maternal endothelial cells. Regenerative endothelial activation is one of the vascular disorders associated with diseases such as high blood pressure. With these descriptions, a two-stage classic model for preeclampsia syndrome has been introduced in which the defect in the conversion of spherical arterial pairs leads to oxidative stress. This condition releases some of the factors into the maternal circulation system and activates endothelial cells. Laboratory studies have shown that oxidative stress is a stimulant to release certain cytokines and pro-inflammatory factors from trophoblast (17).

In addition to identifying the role of oxidative stress as one of the key phases in the preeclampsia, this syndrome is associated with an intensified inflammatory response. Of course, it should be noted that all pregnancies are associated with a systemic maternal inflammatory response, in which peripheral granulocytes, monocytes and lymphocytes increase during the third trimester of pregnancy. This condition intensifies in preeclampsia pregnancies, and some pro-inflammatory factors in the maternal circulation and cytokines that activate the endothelial cells increase (18).

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