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# Contemporary Understanding of Etiopatogenesis of Preeclampsia

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## *Abstract*

Cardiovascular adaptations to pregnancy are essential to assure delivery of oxygen and nutrients to the placenta and fetus. Preeclampsia is a common (5-8% of all pregnancies) disorder of human pregnancy where the normal homodynamic development is compromised. The recent studies ascertain that abnormal migration of trophoblasts early in pregnancy predispose later pathologic changes in vascular endothelium function. Circulating factors produced during reduced perfusion of placenta may impair maternal vascular endothelial function, which in turn will cause such a systemic maternal response as preeclampsia. Endothelial cell dysfunction is considered to play a central role in pathogenesis of preeclampsia. The syndrome is pathophysiologically similar to generalized intravascular inflammatory reaction of maternal body to pregnancy. It is now determined that as a component of non-specific immune defense activated leukocytes produce various reactive oxygen species, such as peroxides, hydroxyl radicals, etc. Normally, when the oxidant-antioxidant system is under appropriate control free radicals are a part of numerous physiologic metabolic processes in the organism. Disbalance of this system induces a vicious circle of a variety of pathologic deviations. Many different clinical, bio-chemical and pathophysiological peculiarities of preeclampsia may be explained by the mechanisms of increased oxidative stress and lipid peroxidation. The relations of the factors, stimulating development of the given pathologic syndrome, to placenta is not yet studied well. Considering the scientific information stated below we are conducting the research aimed to study placental antioxidant system during normal pregnancy and preeclampsia. We are using a complex approach to the processes that take place in placenta so that to link to each other the changes on antioxidant and morphologic levels.

***Keywords:*** *preeclampsia, placenta, endothelium, free radicals, oxidative stress, nitric oxide*

Less than 25 years ago, research in preeclampsia was still sporadic as multidisciplinary study of this problem was not appropriately coordinated, and the International Society for the Study of Hypertension in Pregnancy was only founded near the end of nineteen seventies. All of this "lethargy" was present despite the fact that preeclampsia was and remains a leading cause of morbidity and mortality to both mother and fetus. An exponential increase in the amount of progress made in the field followed the first attempt to focus attention of scientists on the needs of complex understanding, preventing and managing this malicious syndrome. Thus, we are now a more closer towards unraveling the pathogenesis and pathophysiology of preeclampsia.

Cardiovascular adaptations to pregnancy are essential to assure delivery of oxygen and nutrients to the placenta and fetus. Preeclampsia is a common (5-8% of all pregnancies) disorder of human pregnancy where the normal hemodynamic response to pregnancy is compromised. [1,2] Abnormal fetoplacental circulation in preeclampsia furthermore is one of the major causes of intrauterine growth restriction (IUGR) that adversely

affects survival and is explained by impairment of fetoplacental metabolism. [2,5,6]

Preeclampsia remains a leading cause of maternal morbidity and is associated with a five-fold increase in perinatal mortality. [1,2,6] It is known that preeclampsia occurs predominantly among primiparous women increases the risk of iatrogenic prematurity, adverse neonatal outcome and perinatal death. [2,3,6,8,10] Both the etiology and pathophysiology of preeclampsia are poorly understood, therefore neither relevant effective screening or diagnostic tools to reveal this devastating illness at early stages of the development, nor perfect treatment standards are available to prevent its consequences. [2,5] Preeclampsia is diagnosed primarily by the onset of hypertension and proteinuria during the second half of gestation. The fundamentals of diagnosing preeclampsia include a generalized vasoconstriction, increased vasoactivity, reduced perfusion to organs and platelet activation. [2-4] Thus, preeclampsia is believed to be a multisyndrome of complex disorders, which is most likely to be a result of heterogeneous cause. [9,11]

The recent studies ascertain that development of preeclampsia relates to reduced invasion of trophoblast into the maternal endometrium. [12-17] Impaired invasions of trophoblasts due to inadequate oxygenation of maternal endothelium during implantation lead to insufficient circulation and placental ischemia. [18] It is theorized that genetic, [19,20] immune [21,22] and other factors make a considerable contribution to early deterioration of this process. Studies suggest that for different reasons during preeclampsia non-specific inflammatory responses take place in endometrium, which is manifested by production of cytokines, growth and tumor narcotizing factors by various immunocompetent cells. Solidary influence of these factors predetermines coordination of complex processes of metabolism, circulation and development of placental tissue. [1,23-29] Thus, by now it is known that abnormal migration of trophoblasts early in pregnancy predispose later pathologic changes in vascular endothelium function.

J.M. Roberts was the first who in 1989 suggested the conception of endothelial aberration as the keystone of pathology in development of preeclampsia. [31] Since then the theory was evolved that circulating factors produced during reduced perfusion of placenta may impair maternal vascular endothelial function, which in turn will cause such a systemic maternal response as preeclampsia. [2,12,41] According to the last ten years of exploration the most common provocative circulating factors include free fatty acids, lipoproteids, lipid peroxides, cachexin, products of fibrin degradation and, especially, syncytiotrophoblast microvilli fragments shed into the maternal circulation. [5,25,31-40] Placenta represents the main source of the provocative factors and the fact that it is absolutely crucial to develop clinico-phathological alteration typical for preeclampsia provides evidence for its substantial role. [28,42-45] Importance of placenta in etiology and pathology of preeclampsia has been obtained from numerous clinical and biochemical observations. Preeclampsia can occur in the absence of a fetus as molar pregnancy demonstrates. Furthermore, the risk of preeclampsia is increased in conditions with a large or abnormal placenta and also retention of placental tissue may cause the pathologic process to persist postpartum until it is totally removed from the maternal organism. [2,5,28] All the above mentioned proves that placenta plays a fundamental role in developing preeclampsia and therefore precise study of damaging processes in placental tissue excites more and more interest.

The progress achieved in research related to preeclampsia uncovered the key mechanisms of normal fetoplacental vascularization and disclosed that aberration of this mechanisms takes place during preeclampsia. These findings indicate that specialized placental cells called cytotrophoblasts, which are involved in grafting the embryo onto the mother and establishing a blood supply, change their cell surface adhesion receptors from epithelial to endothelial during uterine invasion and vascularization processes. This development does not fully occur in preeclampsia. In addition, the investigators have shown that cytotrophoblasts from preeclamptic placentas that are in direct contact with uterine cells undergo a high rate of apoptosis, or "cellular suicide," without a compensatory increase in mitosis when compared to normal placenta, [45,46] consequently, the maternal-fetal interface is compromised.

As mentioned above, endothelial cell dysfunction is considered to play a central role in pathogenesis of preeclampsia, which may possibly be a component of more compound aberration of functions of circulatory system cells. It is apparent that malfunction of placental and, possibly preplacental vascular endothelium, which constitutes the basis of clinical picture of preeclampsia is not the cause but the result of this syndrome. More and more researchers now suggest that development of preeclampsia has immuno-genetic origin, that actually it represents one of the forms of maternal response to pregnancy. This is in a certain sense similar to generalized intravascular inflammatory reaction. [27] The inflammatory responses are non-specific and may be incited by any form of tissue damage and immunoconflict. Activation of endothelium is a principal component of inflammatory reactions, which are conditioning increased capillar permeability, aggregation of leukocytes, formation of extravasates, production of chemotaxis factors and acceleration of phagocytosis. [5] In preeclampsia this reaction is generalized and

granulocytes, monocytes and neutrophils are activated in response to the pathologic state, which is followed by increased production of cytokines (tumor necrotizing factor, interleukin-6) and phospholipase- $A_2$.[1,5,23-25,28,47] Activation of leukocytes causes adhesion of leukocytes to the endothelium and local damage of endothelial cells. It is now determined that as a component of non-specific immune defense activated leukocytes produce various reactive oxygen species, such as peroxides, hydroxyl radicals, etc. [5,26] *(Fig.1)*

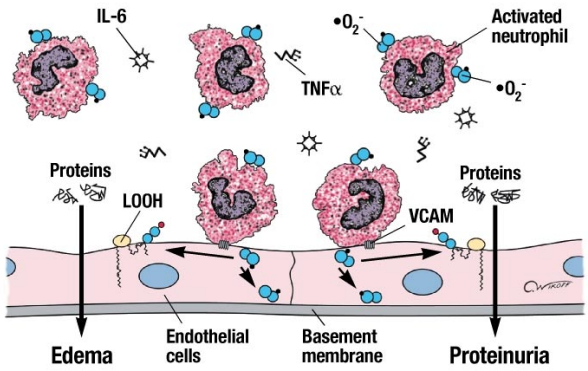


***Fig.1*** *In preeclampsia, leukocytes, such as neutrophils and monocytes, are activated. Inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor (TNF (alpha)), and the vascular cell adhesion molecule (VCAM-1), are elevated in the maternal circulation. Activated neutrophils attach to endothelial cells where they generate superoxide (*02-) resulting in oxidative stress within the cell and lipid peroxidation of the cell membrane (LOOH). This would lead to cell dysfunction. One of the consequences of oxidative stress is increased permeability of the endothelial cells to proteins that would result in edema in the systemic circulation and proteinuria in the kidney.*

Oxygen free radicals, such as superoxide, hydroxyl or peroxide, are chemically active atoms or molecules that have one or more unpaired electrons, which then react with other compounds in order to become stable. In seeking to find stability, they end up damaging the body's tissues, genetic coding and the immune system. Free radicals readily attack lipids, proteins, and DNA resulting in mutations and deleterious effects on membrane and protein structure and function. [5,48,59-60] Normally, when the oxidant-antioxidant system is under appropriate control free radicals are a part of numerous physiological metabolic processes in the organism. They participate in many reactions; they may be interproducts or substrates for a variety of enzymes. [48] Disbalance of this system induces a vicious circle of a variety of pathologic deviations. [49,56]

Antioxidant system withstands free radicals. As it was discovered, the human organism antioxidant system is controlled by superoxid dismutase (Cu-Zn and Mn containing), catalase, selenium containing glutation peroxidase end vitamin E. [47,49,64] When the antioxidant system is broken free radicals react with polyunsaturated fatty acids of membranes or lipoproteins and produce lipid peroxides, which are very important indicators of oxidant stress. [50,51,61-63] *(Fig.2)*

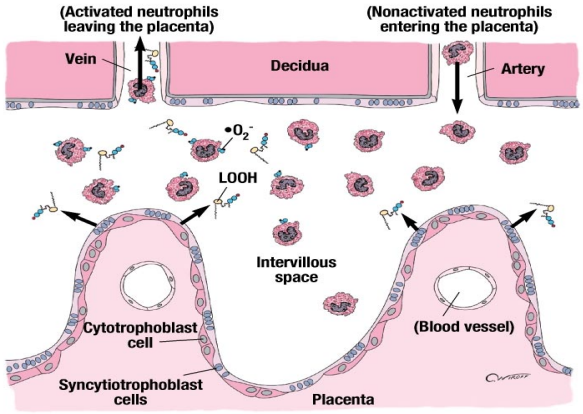


***Fig.2*** *In this hypothesized mechanism for the activation of leukocytes in preeclampsia, increased placental secretion of lipid peroxides would result in activation of leukocytes, such as neutrophils and monocytes, as they circulate though the intervillous space. The activated leukocytes would then enter the maternal circulation where they would generate oxidative stress. Some lipid peroxides might also enter the maternal circulation directly as oxidized fatty acids bound to protein. Both mechanisms would result in an increase in the levels of lipid peroxides in the maternal circulation.*

As studies of various antioxidants in maternal circulation show, women with normal pregnancies have increased oxidative stress, lipid peroxidation and also increased antioxidant protection that offsets the oxidative stress when compared with no pregnant women. [48,50,58] Only a limited number of research works are done by now on placental aspects of oxidant stress, thus, it will be extremely important to study placenta in women having preeclampsia.

In contrast with normal pregnancy, in preeclampsia there is not a sufficient increase in antioxidants to withstand the increase in oxidative stress and lipid peroxidation. In fact, maternal circulating levels of lipid peroxides and placental tissue levels and production rates of lipid peroxides are even further increased in preeclampsia as compared with normal pregnancy.[50,51,57,65]

Various clinical, bio-chemical and pathophysiological peculiarities of preeclampsia may be explained by the mechanisms of increased oxidative stress and lipid peroxidation. Women with preeclampsia have high blood pressure [67] and proteinuria (by definition), many may also develop pathologic edema, [48] besides, leukocyte activation, [23,26] production of inflammatory cytokins, large endothelial cell dysfunction, [69-71] the imbalance of increased thromboxane and decreased prostacyclin, [66] excessive vasoconstriction, reduced uteroplacental blood flow, [33,36,58,66] increased platelet aggregation [68] and platelet adherence to endothelial cells and disseminated intravasclar coagulation are common findings of the syndrome. [5] All of these clinical and pathophysiological components are basically originated from antioxidant-oxidant disbalance.

It is important that some features specific for preeclampsia also take place during normal pregnancy. These are: increase in diastolic pressure and peripheral circulatory volume, decreased platelets and increased uric acid in blood, increased von Willebrand factors, tissue plasminogens and activation of Plasminogen-1 Inhibitors, increase of total fibrinogen concentration in plasma and increased excretion of albumins in urine. It gives an impression that during the last weeks of gestation pregnant women are at increasing risk of developing preeclampsia. As known, pregnancy is a condition with suppressed immunity. [5] However, for unknown reason maternal systemic inflammatory reaction may be stimulated, which is followed by multisystemic dysfunction. The relation of such stimulating factors to placenta is not yet studied well, even though many researchers look for possible links between circulating factors and development of the syndrome and many suppose, that these factors have placental origin. As it is suggested, placenta plays a central role in developing maternal response to pregnancy and processes that take place in placenta are predisposing development of preeclampsia.

Taking into consideration all the above-stated, we have started the research aimed to study placental antioxidant system during normal pregnancy and preeclampsia. We are using a complex approach to the processes that take place in placenta so that to link the changes on antioxidant and morphologic levels. This should be very important in revealing molecular aspects of development of the given pathology and determining effective methods of pathogenic treatment methods.

Pro- and anti-oxidant systems are studied with the method of electroparamagnetic resonance (EPR), which is based on the ability of compounds (in our case placental tissue) placed in the magnetic field of a certain voltage to absorb electromagnetic energy.

We are specifically interested to determine the level of NO in placenta in comparison with normal pregnancy, spontaneous and induced abortions in order to analyze placental tissue redox-potential and homeostasis in early and late, in normal and preeclampsia complicated pregnancies. Recent studies have discovered close interrelations between many different pathologic conditions (hypoxia, stress, inflammation, ischemia, etc.) and excessive production of reactive oxygen species. Many evidences are provided for adverse effects of free radicals on pathogenesis and pathophysiology of numerous diseases (atherosclerosis, cancer, neurodegenerative diseases, sepsis, autoimmune conditions etc.) [59,72,73] Based on review of available literature, we can suggest that our research is novel and gives an opportunity to make thorough conclusions regarding pathogenesis of preeclampsia.

As we have mentioned, NO comprise a particular interest of our study. The researches made since 1992 when Association for the Advancement of Science named nitric oxide "The Molecule of the Year" have confirmed the critical role of NO in functions and dysfunctions of practically all the systems in the body and particularly in endothelial cell dysfunctions. NO is produced in endothelial cells by an enzyme called nitric oxide synthetase (NOS) in response to tissue demands. For example, when an infection occurs NO is produced at the sight of infection and stimulates leukocytes to attack the invading organisms. Besides, it became clear that the mechanism of smooth muscle relaxation is also affected by nitric oxide, and simultaneously the question arose whether during preeclampsia NO concentration may be decreased. [7,72] By now this issue remains to be controversial. Some researchers suggest that the level of NO is really decreased, however, some believe, that excessive arteriolodilatation early in pregnancy proves the opposite. Based on the above mentioned, we have decided to determine the level of NO in placenta, which we envision as one of the major determinants of development of clinical picture of preeclampsia.

Finally, complex influence of placental factors results in systemic manifestations of preeclampsia. Therefore, we may suppose that pathologies changes in placenta followed by production of circulating factors are contributing to dysfunction of endothelial cells, which reduces perfusion to organs (including placenta). Oxidative stress also significantly affects endothelial regulatory mechanisms. We believe, that interaction of various factors may take place in preeclampsia causing dysfunction of endothelium. We also think that endothelial damage is a part of a larger intravascular inflammatory response, which causes the clinical development of preeclampsia. Our research focuses on such specific mediators of vascular dysfunction, which may play a predominant role in preeclampsia. Possibly, the role of these mediators is not necessarily to be

discussed from the point of view of etiopathogenesis of the preeclampsia, but in attempt to develop mechanisms, which will prevent development and dissemination of the destructive processes of the syndrome. Better understanding of these processes will give further an opportunity to discover therapeutic interventions to weaken and slower progress of preeclampsia in order to assure normal development of the fetus and avoid maternal complications.

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# Современное понимание этиотатогенеза преэклампсии

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## Р Е З Ю М Е

Сердечно-сосудистая адаптация к беременности имеет существенное значение для обеспечения плаценты и зародыша кислородом и питательными веществами. Преэклампсия является частой патологией беременности (в 5-8% случаев), во время которой нарушена нормальная гемодинамическая реакция организма на беременность. Недавними исследованиями было установлено, что патологическая инвазия трофобласта на ранней стадии беременности предрасполагает к развитию более поздних патологических изменений функции сосудистого эндотелия. Циркулирующие факторы, продуцируемые во время уменьшенной перфузии плаценты, нарушают функцию материнской сосудистой эндотелиальной системы, что, в свою очередь, вызывает мультисистемный материнский ответ в виде преэклампсии. Эндотелиальная дисфункция клеток играет центральную роль в патогенезе преэклампсии. Этот синдром подобен генерализованной внутрисосудистой воспалительной реакции материнского организма на беременность. Определено, что в качестве компонента неспецифической иммунной защиты активизированные лейкоциты способны производить различные реактивные соединения кислорода (такие, как пероксиды, гидроксильные радикалы и т.п.). Обычно, когда антиоксидант-оксидантная система находится под соответствующим контролем, свободные радикалы участвуют в многочисленных физиологических метаболических процессах организма. Дисбаланс этой системы создает порочный круг различных патологических отклонений. Многие клинические, биохимические и патофизиологические особенности преэклампсии можно объяснить механизмами увеличенного окислительного стресса и пероксидации липидов. Отношение факторов стимулирующих развитие патологического синдрома к плаценте, все еще недостаточно изучено. Наши исследования направлены на изучение плацентарной антиоксидант-оксидантной системы при нормальной беременности и преэклампсии. Мы используем комплексный подход к процессам, имеющим место в плаценте, с тем, чтобы логически связать друг с другом изменения на антиоксидант-оксидантном и морфологическом уровнях.

***Ключевые слова:*** *преэклампсия, плацента, эндотелий, свободные радикалы, оксидационный стресс, окись азота*