DOI: 10.5281/zenodo.1299020
UDC: 618.3-06:616.8-009.24:612.015.11

The oxidative stress in preeclampsia

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Abstract

Background: The pathogenesis theories of preeclampsia include inappropriate trophoblast invasion and incomplete remodeling of spiral uterine arteries. This is followed by a reduced utero-placental perfusion; ischemia is the cause of oxidative stress activation. The imbalance between the oxidant and antioxidant components in favor of pro-oxidation, induce endothelium activation and / or dysfunction with the occurrence of clinical and laboratory manifestations.

Material and methods: It was proposed a comparative prospective study including 105 pregnant women with preeclampsia in comparison with 367 pregnancies without preeclampsia. Pro-oxidant and antioxidant status and its correlation with systolic blood pressure values and classical laboratory marchers were analyzed.

Results: In preeclampsia there is an excess accumulation of pro-oxidants comparing to control group p<0.001**.** Malondialdehyde and Advanced Oxidation Protein Products are most implicated in hypertensive syndrome r 0.7, p<0.001. Inflammatory diseases of uro-excretory tract accompanying preeclampsia, demonstrate excess accumulation of Advanced Oxidation Protein Products and AGE verprelizine-like and AGE pentozidine-like r 0.7, p<0.001. Modified ischemic albumin did not get the modified value in the research group.

Conclusions: Excess accumulation of pro-oxidants in preeclampsia plays an important role in pathogenesis pathway, clinical and laboratory manifestation of preeclampsia.

Key words: preeclampsia, oxidative stress, pro-oxidants, hypertension, proteinuria.

Introduction

Preeclampsia (PE) is a heterogenic and multisystem pathologic condition appeared in pregnancy, characterized by hypertension and commonly accompanied with proteinuria after 20 weeks of gestation. It is mediated by endothelial dysfunction, vasospasm and implication of one or more organs inclusively utero-placentar system [1].

One of actual PE etiology theories is poor trophoblast invasion and improper spiral arteries remodeling, preceded by reduced utero-placentar perfusion, ischemia which is the principal cause of oxidative stress imbalance in favor of pro-oxidants [2, 3]. The most important effect of pro- oxidants excess in PE is endothelial damage [4], vasospasm and increased peripheral resistance [5].

Relevant to PE pro-oxidative factors are: Advanced Glycation End Products, Advanced Oxidation Protein Products, Malondyaldehide, and Ischemic Modified Albumin. All of them are known to have a negative endothelial effect.

Advanced Glycation End Products bind to their receptor (RAGE) and alterate the invasion of trophoblast and placenta, activating general inflammatory pathway and local inflammatory response being responsible for the placental dysfunction and IUGR in PE [6,7, 8].

Advanced oxidation protein products are considered a biomarker of oxidative stress known to be in excess in different metabolic syndromes and kidney diseases. It plays an important role in endothelial dysfunctions and proteinuria [9]. Also it's suggested that AOPP are accumulated in placenta and play a negative role in trophoblast invasion and increases apoptosis [10, 11].

Malondyaldehide is a result of lipid peroxidation which results in oxidative stress. Lipid peroxides are considered to be toxic for endothelial cells, increase the synthesis of tromboxane with a decrease of prostacyclin synthesis with resulted vasoconstriction [12]. Excess of Malondyaldehide in PE is the cause of accumulation of reactive oxygen species and free radicals accumulation are involved in endothelial lesions [13]. So, all of pro-oxidants discussed manifesting endothelial injury and vasoconstriction are responsible for clinical and laboratory manifestations of PE as hypertensive syndrome, and proteinuria.

As antioxidant capacity are discussed Total Antioxidant Activity and Cupric Ionic Oxidation Capacity. The results of most studies indicate a decrease of antioxidant factors in PE [14, 15].

Material and methods

It was proposed a comparative prospective study which included sample research in 105 pregnant women with preeclampsia and comparative sample in 367 pregnant women without preeclampsia. Including criteria in research sample were: singleton gestation with 27-41weeks gestation with preeclampsia. Excluding criteria were: multiple pregnancies, diabetes, superimposed preeclampsia, congenital malformations of the fetus and pregnancy with rhesus conflict. Including criteria for comparative sample were: singleton pregnancy without preeclampsia. Excluding criteria were: multiple pregnancy, diabetes, congenital malformations of the fetus and pregnancy with rhesus conflict.

The following pro-oxidant parameters were determined in our research: advanced oxidation protein products (AOPP), advanced glutathione end products verprelizine-

like (AGE-Verpelizine-like) and advanced glutathione end products pentozidine-like (AGE-Pentozidine-like), Malondialdehyde (MDA). Antioxidant effect was studied based on total antioxidant capacity (TAC) and cupric ionic reducing capacity (CUPRAC).

The values of systolic blood pressure were measured 4 times, every 6 hours daily. The results were introduced in data base ACCESS.

Results and discussion

First of all was studied the balance of oxidative stress in preeclampsia. As it is known, PE is a disease associated with an imbalance between pro-oxidant and antioxidant parameters of oxidative stress [15, 16, 17]. Comparative results of these parameters were set out in the table below:

Table 1

Average values of pro-oxidants and antioxidants of oxidative stress in the research and comparative groups (Media, SE, p)

Pro-oxidant/antioxidant factor	Research sample	Control sample	P
Advanced oxidation protein products	173.4±17.1	46.4±7.8	0
AGE verprelizine like	1209.5±201.5	349.9±26.3	0
AGE pentozidine like	2137.1±179.7	529.6±37.1	0
Malondialdehyde	34.5±4.0	18.3±2.2	0
Total antioxidant activity	8.8±16.7	8.1±10.6	0.9
Cupric ionic oxidation capacity	1.9±0.3	3.5±0.4	0.1
Ischemic modified albumine	0.4±0.1	0.4±0.1	0.3

As can be seen in the table, the mean values of pro-oxidant substances in PE are significantly different compared to these values in the control group. But the mean values of antioxidant substances are similar in both groups. Thus, we can deduce that PE is associated with an imbalance of oxidative stress in favor of pro-oxidants at a concentration of antioxidants similar to the control group [15, 18]. According to Burton G.J. and other authors, pro-oxidants play a major role in pathophysiology of different pathologies including PE. Because of superficial invasion of trophoblast and endothelium activation the placental barrier is broken, creating a leakage of pro-oxidants and placental debris in maternal circulation with activation of inflammatory cascade and accumulation of more pro-oxidants. Accumulated pro-oxidants have a negative effect on maternal endothelium being the most important cause of clinical manifestations of PE [19].

Malondialdehyde and Advanced Oxidation Protein Products are most relevant pro oxidants excess responsible for endothelial cell damage. MOA are the final products of lipids peroxidation. Activated endothelium in cerebral, renal and hepatic system decreases the synthesis of endothelium derived vasodilatations such as Nitric Oxide and increases the synthesis of vasoconstrictors like Endotheliin1 and Tromboxane A2 which are responsible for vasoconstriction and hypertensive manifestations of PE [20, 21].

Based on the above, we assumed the existence of correlation between the higher values of the pro-oxidant markers with first mandatory manifestation of preeclampsia- high values of systolic blood pressure which were measured before labor. As a result, we have achieved an intense and true correlation between these parameters and pro-oxidant markers of oxidative stress r 0.7, p <0.001 in the case of association of the maximum blood pressure measured in the morning and r 0.5, p <0.001 to maximum values of systolic blood pressure at night and at midnight, and r 0.6, p <0.001 at nocturnal systolic blood pressure. Furthermore, the highest values of systolic blood pressure were determined in the morning and in the night.

The next step in our study was evaluation of correlation grade of pro-oxidants with biochemical parameters as total protein, urea, creatinine and fibrinogen blood levels which frequently are pathological in PE.

Table 2

Representation of direct and indirect correlation between pro-oxidants parameters of oxidative stress and blood parameters in preeclampsia (correlation coefficient "r", p)

Pro-oxidant parameter	Biochemical parameter	Correlation coefficient "r"	P
AGE pentozidine like	Proteine in blood	-0.4	<0.0001
AGE verprelizine like	Ureia in blood	0.3	<0.0001
AOPP	Fibrinogen	0.5	<0.0001
AOPP	Creatinin in blood	-0.3	<0.0001
MDA	Proteine in blood	0.3	<0.0001

In terms of the results obtained and presented in the table above, there are various correlations between the pro-oxidant parameters and the biochemical parameters, which denote the systemic involvement of the pro-oxidant substances in the pathogenesis mechanisms of PE. As seen in the table above, there is obtained a negative correlation between AGE pentozidine-like marker and total amount of blood protein. With this was demonstrated that low concentration of general blood protein is dependent of high accumulation of AGE pentozidine-like which is known to be implicated in high permeability of endothelium and mediation of inflammation [22]. Another important correlation was found between AOPP and blood concentration of fibrinogen (r 0.5, p<0.0001) which is sugestive for association between inflammation and excessive acumulation of pro-oxidants like AOPP. The next biochemical blood markers as ureia and creatinine demonstrated moderate but sure correlation with AGE verprelizine-like and AOPP which also indicated a moderate implication of pro-oxidants in pathological process of uroexcretor system.

One of frequent diagnostic criteria of PE is proteinuria. The following significant correlations were found between this criteria and pro-oxidants factors: AGE verprelizine-like and AGE pentozidine-like were in moderate correlation,

r 0.4, p <0.0001 and AOPP, MDA and proteinuria with r 0.3, p <0.001. An interesting correlation has been found between the presence of bacteriuria in the urine investigation which was significantly correlated with AGE verprelizine-like, AGE pentozidine-like and AOPP: r 0.7, p <0.0001 [23, 24]. In support of the opinion that pro-oxidative factors are accumulating in excess in different independent pathological conditions accompanying pregnancy with PE such as obesity, cardiovascular pathology, inflammatory disease of uro-excretor and genital system, the following significant correlations have been found. AOPP was mostly increased in pregnancy with PE and obesity, F 8.3, p<0.005 but in case of chronic pyelonephritis the values of AGE vertelizine-like and AGE pentozidine-like were significantly increased in the research group compared to their values in the control group, F 15.6, p<0.0001. [25]. In case of cardiovascular and endocrine pathologies there were not found any significant correlations. Moreover, statistically significant correlations were found between vertelizine-like AGE concentrations in neo-natal outcome with ischemic brain lesions as compared to women in the research group without this result at birth $\chi 2$ 17.6, p< 0.001[26, 27].

The last discussed pro-oxidant is Ischemic Modified Albumin. There is a contradictory opinion about its role and importance in PE. Some of them consider it an important marker of ischemia while others did not find any correlation with PE in their studies [28, 29, 30]. In our study, no correlation of IMA with clinical and/or laboratory parameters of PE was found.

Conclusions

Our study demonstrates the importance of oxidative stress imbalance in PE in favor of pro-oxidants p<0.0001. Most pro-oxidants implicated in PE have endothelial toxicity effect and promote inflammation mechanisms being responsible for vasoconstriction, hypoxia and hypertension. Inflammation of uro-excretory system (p<0.001) and obesity are the most relevant medical conditions in PE with excess accumulation of pro-oxidants p<0.005. Also we found a moderate correlation between AGE verprelizine- like concentrations and fetal hypoxic brain lesions in PE.

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