

Alterations of Oxidative Metabolism at the Pregnancy Attended with Pre-eclampsia

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ABSTRACT

Numerous facts suggest that diverse complications of pre-eclampsia are caused by pathological changes in the maternal vascular endothelium. Intensification of oxidative stress and nitric oxide deficiency have been thought to play important role in the development of structural and functional changes in vascular endothelium of maternal organism. Hence, our objective is to identify the role of nitric oxide metabolism and oxidative stress in the mechanism of late toxicosis of pregnant. During the pregnancy with pre-eclampsia a significant rise of oxidized ceruloplasmin indicates to the activation of oxidative processes in the organism and lowered antioxidant defense of blood. Oxidation of ceruloplasmin causes also reduction of its ferroxidative activity, which becomes apparent by drastic decrease of Fe^{3+} -transferrin in blood and accumulation of Fe^{2+} ions in blood serum. Fe^{2+} ions are potent promoters of processes of free radical oxidation. Oxidative stress is one of the factors, which favor an activation of nitrosilation by NO of deoxyhemoglobin converting the latter into nitrosohemoglobin (HbNO). This mechanism results in the reduction of the level of free NO and the restriction of its vascular dilating effect. Under the conditions of oxidative stress nitric oxide can also be converted into cytotoxic peroxynitrite, which has high vascular constrictive activity and contributes to the development of vascular endothelial dysfunction and an increase in resistance characteristic for pre-eclampsia. Thus, results of the present study suggest that during the pregnancy attended with pre-eclampsia, the intensification of free radical oxidation (that reveals in blood by disorder of antioxidant defense ceruloplasmin - Fe^{3+} -transferrin enzymatic system function) and the restriction of physiological function of free NO (that results from its conversion into HbNO complexes and peroxynitrite) contribute to an increase in vascular resistance and the development of endothelial dysfunction.

KEYWORDS: pregnancy, oxidative metabolism, pre-eclampsia, nitric oxide, manganese, iron

Organisms of pregnant woman and fetus are especially sensitive to various stress-factors effecting a human being with increasing intensity. Effect of harmful agents causes metabolic disorders, functional disorders of tissues and organs, disorder of fetus-placenta homeostasis, the development of early and late toxicosis of pregnancy, abortion, still birth [9]. Therefore special attention has been paid to the causes and mechanisms of the pathologies of pregnant [2,3,10]. The above-mentioned fully pertains to one of the complications of pregnancy - toxicosis of the late period of pregnancy (hectosis, pre-eclampsia).

So far the etiology and pathogenesis of one of frequent and dangerous complications of pregnancy - late toxicosis (hectosis, pre-eclampsia) has been less studied. Numerous facts suggest that diverse complications of pre-eclampsia, including vascular reactivity alterations, vascular spasm and multiorganic pathologies, are caused by pathological changes in the maternal vascular endothelium [5,6,11].

Intensification of oxidative stress and nitric oxide deficiency have been thought to play important role in the development of structural and functional changes in vascular endothelium of maternal organism [7,8].

Hence, our objective is to identify the role of nitric oxide metabolism and oxidative stress in the mechanism of late toxicosis of pregnant.

MATERIALS AND METHODS

Blood taken from 49 pregnant women with hestation period of 24-36 weeks have been examined. 34 women had pregnancy without any complications (physiological pregnancy) and 15 women - pregnancy with pre-eclampsia. Pre-eclampsia was diagnosed based on criterias of modern classification [4]. In particular, at the end of 20th week systolic arterial blood pressure was

more than 140mmHg and diastolic - more than 90 mmHg. Proteinuria also was revealed.

The intensity of oxidative stress in the body has been discussed based on Electronic Paramagnetic Resonance (EPR) method. For this purpose in blood of the examined women activity of prooxidant (levels of Mn^{2+} , Fe^{2+} , methemoglobin) and antioxidant systems (levels of ceruloplasmin and Fe^{3+} - transferrin) have been measured. In order to study metabolism of nitric oxide we examined levels of free nitric oxide (NO) and NO complexes with hemoglobin in blood. In order to detect free nitric oxide, we used * Natrium diethildithiocarbamat (SIGMA) at dose of 0,35 mg on 200 mcl blood. EPR spectrums have been determined on the radiospectrometrum RE-1307 (Russia) at the temperature of liquid nitrogen.

RESULTS AND DISCUSSION

The table shows changes in blood paramagnetic centers in pregnant women during physiological pregnancy and pathological pregnancy attended with pre-eclampsia (III term). It proceeds from the data presented in the table that in the course of physiological pregnancy intensity of EPR signal of oxidized ceruloplasmin in maternal blood does not undergo any changes compared to controls, EPR signal of Fe^{3+} transferrin is lowered by 10% with statistic certainty compared to controls. During physiological pregnancy in maternal blood changes in the level of free NO do not occur, EPR signals of methemoglobin, Fe^{2+} , Mn^{2+} ions and Mo^{5+} complexes are not revealed.

In the late terms of pregnancy (III term) attended with pre-eclampsia intensity of EPR signal of oxidized ceruloplasmin in the blood is enhanced by 180% compared to controls, intensity of EPR signal of Fe^{3+} - transferrin is significantly reduced to 68% and 77% of those of controls and physiological pregnancy respectively.

	N	CP g=2,05	Fe ³⁺ tr g=4,2	Mn ²⁺ g=2,14	Fe ²⁺ g=2,25	Mo ⁵⁺ g=1,97	MetHb g=6,0	NO	HbNO
1 Healthy - No pregnant Women	50	18,8±0,8	27,8±0,9	-	-	-	-	23,0±1,2	-
2 Healthy - pregnant women during physiological pregnancy (III term)	34	18,5±0,2 p ₁₂ >0,1	25,0±0,3 p ₁₂ <0,02	3,1±0,08	-	-	-	24,09±0,1 p ₁₂ >0,1	-
3 Pregnant women during pathological pregnancy attended with pre-eclampsia (III term)	15	53,2±1,5 p ₁₃ <0,001 p ₂₃ <0,001	19,04±1,0 p ₁₃ <0,001 p ₂₃ <0,001	18,7±0,97 p ₂₃ <0,001	43,06±2,5	14,8±0,5	43,3±3,0	26,8±1,0 p ₁₃ >0,05 p ₂₃ <0,001	45,2±5,0

$$r = 0,609 \quad t = 2,77 \quad s = 0,22 \quad p < 0,02$$

Tab.1 Changes in blood paramagnetic centers in pregnant women during physiological pregnancy and pathological pregnancy attended with pre-eclampsia (III term).

As it proceeds from the data presented in the table, during physiological pregnancy free nitric oxide levels in blood in the III term does not differ from those of healthy women. During pregnancy attended with pre-eclampsia these parameters tend to increase as compared with those of physiological pregnancy (see the table). It also should be pointed out that during the pregnancy attended with pre-eclampsia EPR signals of HbNO complexes are revealed in the blood of examined women. Also, an inverse relation has been found between intensity of this signal (HbNO) and the levels of free NO in blood. During the pregnancy with pre-eclampsia EPR signals of methemoglobin, Fe²⁺, Mn²⁺ ions and Mo⁵⁺ - xanthine oxidase in blood have been recorded.

Ceruloplasmin is a blood serum multifunctional protein. It is characterized with superoxididismutative, peroxidative and ferroxidative activity. Level of Cu²⁺-ceruloplasmin in blood determines its antioxidant activity. In addition, ceruloplasmin functions in the blood as an oxidizer of Fe²⁺ (Fe²⁺>Fe³⁺) and provides Fe³⁺ ions to be inserted in apotransferrin. This process results in elimination of Fe²⁺ ions as immediate inductors of free radical oxidation from blood serum. The operation of two enzymatic systems (ceruloplasmin-transferrin) prevents lipid peroxidation. Diminution of EPR signal intensity of Fe³⁺-transferrin against the unchanged activity of ceruloplasmin detected by us may be attributed to a decrease of iron ion levels in blood and blood serum, characteristic of physiological pregnancy [1]. During the pregnancy with pre-eclampsia a significant rise of EPR signal of ceruloplasmin, detected by us, indicates the activation of oxidative processes in the organism and lowered antioxidant defense of blood. An increase of ceruloplasmin oxidation causes also reduction of ferroxidative activity, which becomes apparent by drastic decrease of Fe³⁺-transferrin in blood and accumulation of Fe²⁺ ions in blood serum.

Interestingly, in the group of pregnant women with pre-eclampsia EPR signals of free iron ions (Fe²⁺) show up against the significant reduction of total iron level in blood [1]. It is known that iron homeostasis is mainly dependent on its absorption in the body and intensity of its utilization. Pregnancy is characterized with intensification of iron utilization, which frequently leads to the development of iron lack anemia. During physiological pregnancy iron deficiency in the organism is compensated by the normal function of blood antioxidant and iron transportation systems (Fe³⁺-transferrin-ceruloplasmin). During pathological pregnancy (pre-eclampsia), against the activation of free radical oxidation, lowered antioxidant defense and iron transportation system deficiency, iron is expected to reduce its participation in proliferative processes and to increase its participation in free radical oxidation processes.

According to the results of our study, during pregnancy attended with pre-eclampsia, EPR spectrum of blood also reveals an increase in signal of Mn²⁺ ions, which leads to the destruction of membrane structures of the body and inactivation of superoxide dismutase.

Fe²⁺ and Mn²⁺ ions are potent promoters of processes of free radical oxidation. They participate in the reactions of Fenton and Haber-Weis and thereby contribute to the formation of large amounts of hydroxyl radicals, intensification of lipid peroxidation, cellular membrane injury (including erythrocytes) and erythrocyte hemolysis that is manifested by intensive EPR signal of methemoglobin in the EPR spectrum of blood. Methemoglobin is an additional source of Fe²⁺ ions that contributes to the development of oxidative stress and augments pre-eclampsia.

Oxidative stress is one of the factors, which favors an activation of inducible NO-synthase. Excessively produced, iNOS-mediated NO easily nitrosilizes

deoxyhemoglobin converting the latter into nitrosohemoglobin (HbNO). This mechanism results in the reduction of the level of free NO and the restriction of its vascular dilating effect. Under the conditions of oxidative stress nitric oxide can also be converted into cytotoxic peroxynitrite, which has high vascular constrictive activity and contributes to the development of vascular endothelial dysfunction and an increase in resistance characteristic for pre-eclampsia.

Thus, results of the present study suggest that during the pregnancy attended with pre-eclampsia, the intensification of free radical oxidation (that reveals in blood by disorder of antioxidant defense ceruloplasmin - Fe^{3+} -transferrin enzymatic system function) and the restriction of physiological function of free NO (that results from its conversion into HbNO complexes and peroxynitrite) contribute to an increase in vascular resistance and the development of endothelial dysfunction.

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Изменения окислительного метаболизма при беременности осложненной преэклампсией

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РЕЗЮМЕ

Принято считать, что многочисленные осложнения преэклампсии, включая нарушение реактивности кровеносных сосудов, вазоспазм и мультиорганные патологии, обусловлены патологическими изменениями в кровеносных сосудах матери. Предполагают, что в развитии структурных и функциональных нарушений в эндотелиуме важная роль принадлежит интенсификации процессов свободнорадикального окисления и недостатку оксида азота. Цель работы - изучить роль окислительного стресса и метаболизма оксида азота в патогенезе позднего токсикоза беременных. Методом ЭПР исследовали состояние про- (содержание ионов Mn^{2+} , Fe^{2+} , метгемоглобина) и антиоксидантной систем (церулоплазмин- Fe^{3+} трансферрин), а также метаболизм оксида азота в крови беременных женщин с физиологическим и патологическим (преэклампсией) течением беременности. Установлено, что в третьем семестре физиологической беременности состояние про- и антиоксидантной системы и содержание свободного оксида азота незначительно отличаются от значений соответствующих параметров, характерных для здоровых небеременных женщин. При преэклампсии в крови беременных женщин наблюдается инактивация антиоксидантной системы (церулоплазмин- Fe^{3+} трансферрин), накопление промоторов свободнорадикального окисления, ионов Mn^{2+} , Fe^{2+} и метгемоглобина. При преэклампсии наблюдается также усиленное нитрозилирование дезоксигемоглобина и образование комплексов HbNO. Последнее способствует ограничению физиологической активности NO, увеличению резистентности кровеносных сосудов, развитию дисфункции эндотелиума, характерных для преэклампсии.

КЛЮЧЕВЫЕ СЛОВА: беременность, окислительный метаболизм, преэклампсия, оксид азота, ионы марганца, ионы железа