

Endothelial Dysfunction As A Predictor Of Changes In System A Mother-Placenta-Fetus At The Complicated Pregnancy Gulchekhra Tastanova

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Abstract: Were elucidate changes in the NO content, eNOS and iNOS activity, ONO_2^- , VEGF, VEGFR-2 rate in the placenta and umbilical cord blood of a newborn after pregnancy with hypochromic anemia and gestosis. In pregnancy, complicated by gestosis and hypochromic anemia, unidirectional disturbances in the NO-system are noted - inhibition of e-NOS activity against the background of NO, i-NOS and ONO_2^- expression. The development of DEP in the mother-placenta-fetus system is combined with the expression of ET-1, VEGF and its VEGFR-2 receptor, which can cause the development of structural disorders in the placenta, disorders of angiogenesis in it and as a consequence the development of placental insufficiency, pre – and postnatal fetal pathology.

Key words: vascular endothelium, angiogenesis, vascular endothelial growth factor, nitric oxide, hypochromic anemia, gestosis.

1. INTRODUCTION

Now days the problem of importance of the endothelial dysfunction (ED) of vessels in formation of pathological process in functional system a mother-placenta-fetus is widely discussed [1,4,11]. Interest in the specified problem is that an angiogenesis in a placenta and a becoming of an uterine-placental and feto-placental blood flow – the key events which are necessary for ensuring the main function of a placenta – exchange of oxygen and nutrients between a maternal organism and the growing fetus [8]. It is established that whether throughout the entire period of a gestation in a placenta with big smaller intensity two processes proceed: vasculogenesis – formation of vessels of their cages predecessors of angioblast and angiogenesis – formation of new vessels from already existing [9]. The modern representation about vascular endothelium underwent some changes, so at the moment endothelium is considered not only as the semi-permeable membrane, but also as the active endocrine organ. The major functions an endothelium - maintenance of a hemo vascular homeostasis, regulation of a hemostasis, inflammation modulation, regulation of a vascular tone and permeability of vessels. In addition, the existence of renin-angiotensin system was revealed. All these functions of endothelium of vessels realizes the blood circulations directed by synthesis, and release of the active different biological agents, which are used for balanced work of the blood circulatory system. An essential role in regulation of a local tone of vessels is played synthesis level in an endothelium of nitrogen oxide (NO) which is formed of L-arginin with participation of a nitric oxide synthase (e-NOS), and at pathological conditions of an inducible nitric synthase (i-NOS) [2]. In the conditions of a hypoxia the surplus in fabrics of super oxidic anion (O_2^-) easily reacts with free NO, forming high-reactionary and toxic connection – peroxynitrit (ONO_2^-)

[6]. Now it is known that from a large amount of biologically active agents, which are secreted by endothelium, nitrogen oxide regulates activity of other mediators [7].

The important regulator of a tonus of vessels and level in an endothelium is endothelium (ET-1) – an endothelial vasopressor peptide [4,9]. Now ET-1 is surveyed as a marker and a predictor of many pathologies, such as coronary heart disease, acute infarct, atherosclerosis, hestosis, feto-placental failure [1,14]. The essential role in development of angiogenesis belongs to growth factor an endothelium of vessels (VEGF) [16]. VEGF realizes the angiogenic effects through the specific tyrosine kinase receptors located on a surface of endothelial cages – VEGFR – 1 (flt-1) and VEGFR-2 (flt-1/KDR) [11,17]. It is established that on endothelial cages mainly expresses VEGFR-2 and, apparently, VEGF carries out the biological effects through linking with these receptors [3,16]. The inductor of synthesis of VEGF is endogenous NO [5]. There are data that endogenous NO can either oppress, or activate inducible hypoxia VEGF factor gene depending on a redox-condition of a cage [3,10]. Therefore, among the reasons there is development of pathology of pregnancy, pre- and post-natal death of a fetus, can be the processes of the dysfunction endothelium (DE) connected with violations of activity of endothelial system and regulation of angiogenesis at the level of feto-placental blood circulation. Due to above stated, the purpose of our research was to analyse changes of maintenance of NO, activity of e-NOS and i-NOS, the ONO_2^- , VEGF, VEGFR-2 in a placenta and umbilical blood of the newborn after pregnancy with hypochromic anemia and hestosis.

2 MATERIALS AND METHODS OF RESEARCH.

The survey included 81 biological objects: placenta and serum of umbilical cord blood of newborns, which were distributed into 3 groups. Group 1-placenta and umbilical cord blood from 30 women after pregnancy with gestosis (pronounced edema, systolic blood pressure more than 170 mm Hg.St., proteinuria 3 g/l), group 2 – from 31 women after pregnancy with hypochromic anemia (Hb less than 10 g / 100 cm³) and group 3 – control, from women with physiological pregnancy. Births in the control group, at 38-40 weeks of gestation (39.4 ± 2.83

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weeks), proceeded without complications, ended with the birth of a alive child without signs of pathology. In puerperas with gestosis and anemia, labor occurred at 34-38 weeks (36.5±2.9) of gestation with various complications: the development of fetoplacental insufficiency, premature aging of the placenta, premature detachment of the normally located placenta, the threat of premature termination of pregnancy and early childbirth, intrauterine fetal hypoxia, delay in fetal development, spontaneous miscarriages, low placentation. In biopsies and serum levels of NO were determined by the content of its main stable metabolites (NO₂⁻ and NO₃⁻) using Griess reagent [2]. The activity of e-NOS for changing the education product of NO from L-arginine in the presence HADSH [11], the activity of I – NOS by the change of speed of the reaction HADSH-dependent nitroreductase [14], ONO₂⁻ oxidation of hydroxylamine [3]. The level of ET-1, as well as VEGF and VEGFR-2 were determined using the enzyme immunoassay at-858 (LTD., China) using standard kits "Human ET-1", "VEGF Elisa" and "VEGFR-2Ymmunoassan" (R&D System, USA). During comparison and analyzing the interaction of indications used nonparametric and parametric tests: U-criterion Hann-Whitney, median test, the test of Spearman's rank correlation. The significance of differences between the groups was considered at p<0.005. For processing of the obtained data was performed using a licensed Statistic's software package (version 5.1 Statsoft).

3 RESULTS AND DISCUSSION

Analysis of the data shows that both placenta and serum umbilical cord blood of newborns after pregnancy with gestosis and anemia showed a statistically significant increase NO concentration against the background of reduced e-NOS activity. However, the level of I-NOS activity and the content of ONO₂⁻ significantly exceeded the data in the control (table.1). It can be assumed that the increase in placenta and umbilical cord blood of newborns NO was associated with the expression of i-NOS, as e-NOS, was depressed. According to literature the expression of i-NOS is accompanied by the synthesis of NO in excess of e-NOS 100-1000 times [5]. With an increase in the level of NO in the placenta and umbilical cord blood of newborns, we associate a significant increase in them ONO₂⁻ [2,13]. According to the literature, the expression of exogenous NO, i-NOS and ONO₂⁻ can serve as one of the main reasons for the development of the vasoconstrictive effect [3], violations of the processes of micro - and macro-circulation, metabolic disorders in the tissues, accelerating the cell apoptosis and necrosis [9]. These data are confirmed in our studies in the morphological assessment of the placental structure of pregnant women with gestosis and hypochromic anemia. It should be noted that in placenta with gestosis, compared with hypochromic anemia, an increase in the volume of interstitial fibrinoid was more often found against the background of thrombosis of the interstitial space, adhesion and deformation of the villi, areas with heart attacks and petrifications, in all placenta, angiomas equally. In placenta with women anemia often found syncytial nodules (kidneys), increasing the number of subepithelial capillaries located in terminal villi. In the same group, in placents is more likely to have a variant of intermediate differentiated villi, placenta of pregnant women with gestosis has a variant of chaotic sclerosed villi in the assessment of pathological immaturity of the placenta (tab.2).

Can put that in the disruption of the structure of the placenta in postpartum women with gestosis and anemia plays a major role expression of VEGF and its receptor VEGFR-2, and Takei ET-1. Increasing the level of VEGF and VEGFR-2 we regard as a compensatory reaction in the placenta to increase its oxygen supply and nutrients. At the same time, it can play a crucial role in stimulating the Pro-angiogenic factor. This process is facilitated by a significant increase in ET-1. Expression of ET-1 leads to vasospasm, stimulation of iNOS, persistent increase in exogenous NO and NO₂⁻, which have a toxic effect on the vessels of the fetoplacental complex. By doing so, the analysis of the obtained data suggests that among many causes in the pathogenesis of placental insufficiency, pre - and postnatal pathology of the fetus during pregnancy, complicated by the development of gestosis and hypochromic anemia are endothelial dysfunction processes associated primarily with impaired synthesis of endothelial nitric oxide (NO) in angiogenesis process. These data are confirmed by morphological changes in the placenta: abnormalities in the shape of the placenta, an increase in the volume of interstitial fibrinoid, subepithelial localization of capillaries in terminal villi, an increase in the number of syncytial nodules, against the background of various variants of maturation of the villous chorion, as well as disorders of macro - and microcirculation in the functional system of the mother-placenta-fetus.

4 CONCLUSIONS

1. Placenta and serum of umbilical cord blood of newborns during pregnancy complicated by gestosis and hypochromic anemia show unidirectional disorders in the NO-system - inhibition of e-NOS activity on the background of NO, i-NOS and ONO₂⁻ expression.
2. The development of DEP (dyscirculatory encephalopathy) in the mother-placenta-fetus system is combined with the expression of ET-1, VEGF and its VEGFR-2 receptor.
3. The development of DEP in the system mother-placenta-fetus, expression of ET-1, VEGF and its receptor VEGFR-2 can serve as an important reason for the development of structural changes in the placenta, disorders of angiogenesis, and as a consequence the development of placental insufficiency, pre – and postnatal pathology of the fetus during pregnancy complicated by preeclampsia and hypochromic anemia.

5 Table 1. The indicators of activity NO system and of regulators of angiogenesis in serum of umbilical blood of newborns, and biopsy of the placenta in physiological and complicated pregnancy, M±m

Indicator	Control, n=20		Gestosis, n=30		Anemia, n=31	
	inblood serum	inplace nta	inblood serum	inplace nta	inblood serum	inplace nta
NO, $\mu\text{mol/l}$	36,6 \pm 2,27	55,7 \pm 4,07	59,4 \pm 3,62*	130,9 \pm 6,25*	55,1 \pm 2,87*	122,8 \pm 6,30*
e-NOS, $\mu\text{mol/l} / \text{min}$	44,3 \pm 2,39	106,2 \pm 5,84	21,9 \pm 1,45*	58,7 \pm 4,75*	20,6 \pm 1,11*	59,4 \pm 3,38*
i-NOS, $\mu\text{mol} / \text{min}$	0,40 \pm 0,020	0,12 \pm 0,005	3,50 \pm 0,203*	0,65 \pm 0,037*	296 \pm 0,145*	0,72 \pm 0,039*
ONO ₂ ⁻ , $\mu\text{mol/l}$	0,15 \pm 0,008	0,06 \pm 0,003	1,79 \pm 0,093*	2,80 \pm 0,174*	1,90 \pm 0,145*	2,91 \pm 0,166*
VEGF, petagras/ml	103,2 \pm 7,22	238,5 \pm 17,16	339,5 \pm 20,04*	370,1 \pm 22,94*	291,6 \pm 18,95*	358,5 \pm 17,56*
VEGFR-2, ng/ml	3,92 \pm 0,15	7,72 \pm 0,43	5,79 \pm 0,28*	9,87 \pm 0,51*	4,85 \pm 0,32*	10,60 \pm 0,60*
Et-1, petagras/ml	0,53 \pm 0,03	2,19 \pm 0,12	1,62 \pm 0,09*	4,23 \pm 0,22*	1,77 \pm 0,08*	3,96 \pm 0,25*

* - P<0.05 compared to control

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