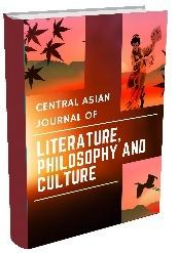

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New Indications of Endothelial Dysfunction-Predictors of Recurrent Obstetric Bleeding

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ANNOTATION

The main indicators of resume endothelial dysfunction are endothelin-1 (et-1), nitric oxide (no), E-selectin and vascular endothelial growth factor (VEGF). The current pregnancy clinical course was studied at 32 in 53anamnes of masiv kon in 32 of the departed fetters and at 32 of the healthy fetters in the control group, the endothelial dysfunction indicators hitandildai. In this regard, we decided to divide them into 2 groups: without the risk of falling, with the risk of falling. An individual analysis of the indicators of endothelial dysfunction showed a pronounced dysfunctional state in pregnant women of the group at risk of miscarriage. In 18-24 weeks of pregnancy, an increase in serum levels of pregnant women et-1 , no, Eselektin and VEGF in relation to the indicators of women with a physiological course of pregnancy was found to be 1.66; 1.2; 1.32 and 1.17 times. In pregnant women at risk of miscarriage, this excess was 3.33; 1.59; 1.72 and 1.68 times. It must be said that in this group of pregnant women, the level of et-1, no, E-selectin and VEGF is 2; 1.32; Pregnant women showed 1.31 and 1.44 times more values without the risk of miscarriage.

KEYWORDS: massive obstetric bleeding, operations, endothelial dysfunction, endothelin-1, nitric oxide, selecine, growth factor, preeclampsia, risk of premature birth.

Relevance Recently, vascular endothelium plays a very important role in the development of vascular disorders. It performs barrier, secretory, hemostatic, vasotonic functions (1,2,3). In many pathological conditions, including complicated pregnancy, the endothelium reacts to various humoral changes in the internal environment by producing vasoconstrictor and vasodilator factors, adhesion molecules, the balance of which determines the tone of smooth muscle cells, being very important in the regulation of vascular tone. Among the numerous factors of endothelial origin, the recognized markers of endothelial dysfunction are nitric oxide (NO) and angiotensin converting enzyme (5,6). In addition, in recent years, great importance in the development of endothelial dysfunction has been attached to endothelins, which can both directly and indirectly influence changes in vascular tone through the generation of nitric oxide and the formation of angiotensin II. The main indicators of endothelial dysfunction are endothelin-1 (ET-1), nitric oxide (NO), E-selectin and vascular endothelial growth factor (VEGF) (5,7). However, it should be said that the values of pregnant women varied widely. Therefore, we decided to analyze the results obtained individually for each pregnant woman, taking into account the presence of obstetric complications of this pregnancy. The purpose of the study. Identification of new indicators of endothelial dysfunction as predictors of recurrent obste Material and methods The clinical course of the present pregnancy was studied in 32 of 53 examined pregnant

women who had a history of massive bleeding, proceeded without complications, and in 38 pregnant women the threat of non-gestation was revealed. In this regard, we decided to divide them into 2 groups: without the threat of not bearing, with the threat of not bearing. An individual analysis of the indicators of endothelial dysfunction showed a pronounced dysfunctional state in pregnant women of the group at risk of not bearing. Result and discussion The conducted studies have shown that pregnant women who have had a history of massive bleeding, at 18-24 weeks of pregnancy, serum levels of ET-1, NO, E-selectin and VEGF increased by 2.33 (P<0.001); 1.2 (P>0.05); 1.48 (P<0.05) and 1.37 (P<0.01) times relative to the indicators of women with a physiological course of pregnancy (Table 1). The analysis showed that the course of a real pregnancy in 32 of 53 examined pregnant women who had a history of massive bleeding proceeded without complications, and 38 pregnant women were found to be at risk of miscarriage. In this regard, we decided to divide them into 2 groups: without the threat of miscarriage and with the threat of miscarriage. An individual analysis of the indicators of endothelial dysfunction showed a pronounced dysfunctional state in pregnant women of the group at risk of miscarriage. So, if at 18-24 weeks of pregnancy in the blood serum of pregnant Dynamics of changes in indicators of endothelial dysfunction in pregnant women who had a history of massive bleeding, M±m Group ET-1, fmol/ml NO, mmol/l E-selectin, ng/ml VEGF, pg\ml Control group 0,605±0,018 15,77±0,38 28,06±1,13 140,16±1,65 comparison group, 18-24 weeks of pregnancy Without threat of miscarriage 1.00±0.09 a 18.99±0.91 37.05±1.38 a 163.49±6.85 a Threat of miscarriage 2.00±0.21a,b 25.05±1.19 a 48.40±0.74 a 236.13±4.10 a,b total, n=53 1.40±0.15 a 21.41±1.09 a 41.59±1.62 a 192.54±11.50 A comparison group, 37-39 weeks of pregnancy Without preeclampsia 1.28±0.22 a 22.18±2.58 a 38.56±2.38 a 176.34±10.81 a preeclampsia 2.24±0.24 a,b 25.76±2.58 a 51.96±2.86 a,b 280.84±28.55 a,b total,n=20 1.85±0.19 a 24.33±1.58 a 46.60±2.44 a 239.04±20.94 a Note: a – differences between the indicators of the main and control groups are significant (P<0.05), b – differences between the indicators in subgroups with and without threat, as well as with preeclampsia and without preeclampsia are significant (P<0.05). Consequently, the indicators of endothelial dysfunction increased more markedly in pregnant women at risk of miscarriage. Analyzing the results obtained, it must be said that all the indicators studied by us play an important role in the development of endothelial dysfunction and are interrelated. Thus, in our studies, a sharp increase in vascular growth factor by 1.68 (P<0.01) times was shown relative to the values of the group of women with the physiological course of pregnancy. Under these conditions, fetoplacental insufficiency and hypoxia develop, contributing to the activation of vascular growth, in which the endothelium takes an active part. In a stable state, endotheliocytes do not proliferate. Under the influence of angiogenic growth factors and cytokines, endotheliocyte proliferation is activated, which ends with their differentiation and further maturation of the vessel or its remodeling, after which the newly formulated vessel becomes stable. The second molecule analyzed by us, NO - exerts a against vasoconstrictor action of endothelins. However, in our studies, the level of ET-1 increased by more than 3 (P<0.001) times, while the level of nitric oxide only by 1.59 (P<0.01) times, which is clearly not enough to eliminate vasoconstriction. It should be said that activation of the expression of endothelial adhesion molecules, in particular E-selectin, plays a great role in the mechanism of endotheliocyte migration. E-selectin is expressed by endothelial cells and is involved in stopping neutrophils (the first stage of migration). It serves as a chemotactic signal for neutrophils and additionally activates β2-integrins, which leads to increased migration of cells containing these integrins, so we observed its increase by 1.72 (P<0.01) times relative to the values of the group of women with the physiological course of pregnancy. The process of angiogenesis is necessary for long-term adaptation of tissues in conditions of damage. In subsequent periods, women with preserved pregnancy (37-39 weeks) who had a history of massive bleeding maintained high values of endothelial dysfunction. Thus, in all 20 examined women, the level of ET-1 in the blood serum increased statistically significantly by 1.32 (P<0.05) times

relative to the values of the previous period and was significantly higher by 3.1 (P<0.001) times than the values of pregnant women with a physiological course. The values of nitric oxide and E-selectin remained within the values of the previous study period, exceeding the values of the control group of pregnant women by 1.54 (P<0.05) and 1.66 (P<0.05) times. At the same time, the content of VEGF, as well as the level of ET-1 increased by 1.24 (P>0.05) times relative to the values of the previous study period. This indicator significantly exceeded the values of the group of pregnant women with a physiological course by 1.71 (P<0.01) times. However, it should be said about the high individual variability of the studied indicators. In this regard, we analyzed individual indicators depending on the course of a real pregnancy. Since preeclampsia was the most common concomitant obstetric pathology in this group, we divided the group into 2 subgroups: without preeclampsia and with preeclampsia. Studies have shown that in pregnant women without signs of preeclampsia at 37-39 weeks of pregnancy, serum levels of ET-1, NO, E-selectin and VEGF increased by 2.13 (P<0.05); 1.41 (P<0.05); 1.37 (P<0.05) and 1.26 (P>0.05) times relative to indicators of women with the physiological course of pregnancy. In pregnant women with preeclampsia, this excess was 3.73 (P<0.001); 1.63 (P<0.01); 1.85 (P<0.01) and 2 (P<0.001) times, respectively. It should be said that in this group of pregnant women, the level of ET-1, NO, E-selectin and VEGF is 1.75 (P<0.001); 1.16 (P>0.05); 1.35 (P<0.05) and 1.59 NO, E-selectin and VEGF were 1.75 (P<0.001); 1.16 (P>0.05); 1.35 (P<0.05) and 1.59 (P>0.05) times the values of pregnant women without clinical manifestations of preeclampsia. Consequently, in pregnant women who have had a history of massive bleeding, manifestations of endothelial dysfunction persist in subsequent pregnancy both in early and late pregnancy. This, in our opinion, predisposes to the risk of microcirculation disorders in the maternal side of the placenta, causing the development of miscarriage in the early stages or preeclampsia – in the later stages of gestation. In our opinion, to assess the state of the vascular endothelium, it is advisable to determine the level of ET-1 and VEGF in the dynamics of gestation.

Analyzing the data obtained, we can say that the main mechanism for the development of preeclampsia is placental insufficiency due to inadequate remodeling of the maternal vascular network in the interstitial space. This stimulates the placenta to release vasosuppressors and other soluble factors into the maternal bloodstream in order to activate the maternal body to create more efficient fetal circulation. However, this leads to systemic endothelial dysfunction of the mother's body and the development of hypertension, proteinuria, the manifestation of disorders of the functions of the brain and other organs and systems in pregnant women with preeclampsia. Based on the results obtained, we have developed an algorithm for pregravidar preparation of women who have suffered massive bleeding. To assess the effectiveness of the proposed therapy on the functional and metabolic parameters of endotheliocytes of pregnant women who suffered massive bleeding, they were divided into 2 groups: those who received therapy for the prevention of complicated pregnancy (group 1A) and those who did not receive treatment (group 1B). The studies were conducted at 18-24 and 27-37 weeks of pregnancy. Studies have shown that in pregnant women who had a history of massive bleeding and did not receive pre-gravidar prophylaxis, at 18-24 weeks of pregnancy, the serum levels of ET-1, NO, E-selectin and VEGF were statistically significantly higher at 2.35 (P<0.001); 1.54 (P<0.05); 1.66 (P<0.01) and 1.71 (P<0.01) times relative to the values of the group of women with the physiological course of pregnancy. That is, this group of pregnant women had endothelial dysfunction, which coincided with the clinical course of pregnancy. In the future (at 27-37 weeks of pregnancy), the level of ET-1 continued to increase, significantly exceeding the indicators of the previous term by 1.3 (P<0.05) times. At the same time, the content of NO, E-selectin and VEGF remained within the values of the previous study period. It should be said that in the blood serum By the end of gestation, the levels of ET-1, NO, E-selectin and VEGF in this group of pregnant women exceeded the values of the group of pregnant women with a physiological course by

3.07 (P<0.001); 1.54 (P<0.01); 1.67 (P<0.01) and 1.74 (P<0.01) times, respectively. Apparently, this was due to the presence of preeclampsia of varying severity during these study periods.

Effect of therapy on indicators of endothelial dysfunction in pregnant women who have had a history of massive bleeding, M±m Group ET-1, fmol/ml NO, mmol/l E-selectin, ng/ml VEGF, pg\ml Control group, n=38 0,605±0,018 15,77±0,38 28,06±1,13 140,16±1.65 1B group without treatment for 18-24 weeks, 1.41±0.085a 24.32±0.83 a 46.59±1.37 a 239.36±12.37 a 1B group without treatment for 27-37 weeks, 1.84±0.11 a 24.33±0.93 a 46.78±1.54 a 243.30±13.88 a 1A after treatment for 18-24 weeks, 0.846±0.048 a,b 15.88±0.34 b 28.51±1.04 b 154.44±3.37 b 1A after treatment 27-37 weeks, 0.695±0.031 a, b 15.87±0.36 b 28.73±1.22 b 147.58±1.94 b Note; a – differences between the indicators of the main and control groups are significant (P<0.05), b – differences between the indicators of the treated and untreated groups are significant (P<0.05).

Analysis of indicators of endothelial dysfunction in pregnant women who had a history of massive bleeding and received pre-gravidar treatment, the development of pronounced endothelial dysfunction was not revealed by us. Thus, only the level significantly exceeded the values of the control group of pregnant women with a physiological course by 1.4 (P<0.05) times, while the indicators of NO, E-selectin and VEGF did not differ significantly from the values of the control group of women. Comparing the values of the indicators of the treated and untreated group of pregnant women, it should be said that the implementation of therapeutic preventive measures significantly reduced the high values of ET-1, NO, E-selectin and VEGF by 1.67 (P<0.01); 1.53 (P<0.01); 1.63 (P<0.01) and 1.55 (P<0.01) times accordingly, relative to the values of the untreated group of pregnant women. In the subsequent periods (27-37 weeks of gestation), the studied indicators continued to decrease and approached the values of women with a physiological course of pregnancy. They did not differ significantly from the values of the previous term. However, compared with the indicators of the group of pregnant women who had a history of massive hemorrhages and did not receive treatment, they were significantly lower. Thus, the level of ET-1, NO, Eselectin and VEGF in the blood serum decreased statistically significantly by 2.65 (P<0.001); 1.53 (P<0.01); 1.63 (P<0.01) and 1.65 (P<0.01) times, respectively. Consequently, pre-gravidar treatment and rehabilitation of pregnant women who have had a endothelium. This has a positive effect on the course of subsequent pregnancy, which coincides with clinical indicators.

Conclusions: Based on the data obtained, the following can be done 1. Pregnant women with a history of massive bleeding develop endothelial dysfunction, manifested by a sharp increase in the level of endothelin-1 in the blood serum, a moderate increase in the content of nitric oxide, E-selectin and vascular growth factor. The severity of these changes increased with the lengthening of the gestation period. 2. The dynamics of changes in indicators of endothelial dysfunction in pregnant women with a history of massive bleeding depended on the course of the current pregnancy, more pronounced in pregnant women with the threat of miscarriage at 18-24 weeks of pregnancy and with preeclampsia at 27-37 weeks of gestation. More indicative is the determination of endothelin-1 and vascular growth factor. 3. Carrying out therapeutic and preventive measures in pregnant women who had a history of massive bleeding leads to a decrease in high values of endothelin-1, nitric oxide, E-selectin and vascular growth factor in blood serum, correction of the dysfunctional state of the endothelium, which leads to a decrease in complications during pregnancy and childbirth.

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