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The clinical value of changes to haemostasis in the pathogenesis of gestational endotheliopathy

Preeclampsia (PE) affects 3–5% of all pregnancies, is a major cause of maternal and fetal morbidity and mortality. The traditional definition of preeclampsia as de novo onset of hypertension and proteinuria after 20 weeks of gestation has been recently modified by the ACOG in recognition of the syndromic nature of preeclampsia. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia, impaired liver function, and new development of renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances[1]. Hypertension, proteinuria, and other systemic manifestations of the syndrome of preeclampsia are the clinical consequences of maternal endothelial dysfunction. Recent data suggest that endothelial dysfunction, vasoconstriction, placental ischemia and enhanced coagulation are associated with abnormal placental development which may lead to inadequate feto-maternal circulation and decreased placental perfusion[2].

Although the pathophysiology of preeclampsia is not fully understood, it is generally regarded as a two-stage disorder. The ability of the uteroplacental vasculature to maintain blood flow at an appropriate rate during gestation can be perturbed by endothelial dysfunction and alterations in vascular smooth muscle cell communication and performance. The first stage consists of reduced placental perfusion, likely due to abnormal implantation and abnormal development of the placental vasculature, because once blood flow leaves the maternal vasculature (and enters the intervillous blood space), shear stress may remodel the developing fetoplacental vasculature (primary gestational endotheliopathy)[3]. In addition, there is a rise in oxygen tension, stimulating cytotrophoblasts to down regulate the expression of adhesion molecules characteristic of their epithelial origin and adopt an endothelial surface adhesion phenotype. The second stage involves widespread endothelial dysfunction resulting in hypertension, proteinuria, and oedema (secondary or generalised gestational endotheliopathy). In normal pregnancies, the spiral arteries are invaded by trophoblastic cells that replace

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the endothelium of these arteries and promote remodelling of the vascular wall with dilation of the blood vessels[1].

The endothelium carries out a lot of the important functions: transport, metabolic, production of cytokines, haemostasis regulation, and maintenance of tonicity and permeability of the vascular wall. It is natural that during its affection all these functions are disturbed. But the most dangerous is dysfunction of haemostasis regulation. Besides, in affection of the endothelium the production of prostacyclin is decreased resulting in loss of the ability of the vascular wall to prevent a vascular spasm, aggregation of thrombocytes and an intravascular thrombosis[2].

In this study, we compared the main ratios of the links to haemostasis system (platelet count, activated partial thromboplastin time, prothrombin index (PI), antithrombin III, and fibrinogen) of normal pregnancy and gestational endotheliopathy (GE). Also we investigated the levels of ADP-induced platelet aggregation.

The reason of our investigation was hypothesis of genesis of perinatal pathology regarding the value of the gestational endotheliopathy as initial factor for disturbances in the haemostasis system.

The study was carried out in the maternity hospital № 1 in Vinnytsya, between 2009–2012. We enrolled pregnant women with GE, who were diagnosed when microalbuminuria was more than 5,0 mg/mmol (screening test), and endothelium-dependent vasodilation was less than 10% (approving test)[3]. All women had singleton pregnancies. The exclusion criteria were: smoking, chronic illnesses such as hypertension, coronary heart disease, renal disease, diabetes mellitus, and fetal malformations.

196 patients were assigned to groups depending on the conditions of investigation. In the first group there were 52 pregnant women with non-manifest form of GE. The second group included 44 pregnant women with clinical manifest form of GE (decidual vasculopathy). 58 health pregnant women, without GE, were included to control group. Also we investigated 42 non-pregnant women.

The platelets were counted in a specific area of the hemacytometer chamber under the microscope. The number of platelets is calculated per μL (x10^9/L) of blood. The PI was derived from measuring [prothrombin time control plasma/prothrombin time patient plasma] x 100. Aggregation was measured by using a photometric method on a 4-channel aggregometer. The activated partial thromboplastin time (APTT), antitrombin III, and fibrinogen were performed using an advanced photoelectronic-double

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magnetic testing system HTI TS4000 Plus, USA. The research of haemostasis system was performed at 10–12 weeks of pregnancy.

Statistical analysis was done on the base of a standard STATISTICA package. Continuous variables, presented as means ± standard deviation (SD), as well as confidence intervals (95%, CI), were tested for normality and frequency distribution and were compared using Student's t-test. The powers of tests were estimated and $p<0,05$ was considered statistically significant.

In the first trimester of pregnancy the indicators of procoagulant haemostasis among patients with gestational endotheliopathy were higher than in a normal pregnancy. But statistically significant increase ($p<0,05$) of the fibrinogen's level relative to non-pregnant volunteers (2669,1 ± 314,2 mg/L) in pregnant women with clinically-manifested GE, was noted in the second group (4254,5 ± 429,9 mg/l). We noted that the concentration of fibrinogen in the II group was higher than women in the control group (3181,0 ± 419,5 mg/l), although it had no statistical significance ($p> 0,05$). In the first group (3461,5 ± 476,2 mg/l) we observed elevated of rate of the fibrinogen relative performance in the control group and non-pregnant women also ($p> 0,05$). This trend was relatively significant difference in the second group compared with the control group was observed regarding PI as the indicator of the external path of clotting. Among pregnant women with endothelial dysfunction, there was no single case of significant increase relative to results of the PI in the control group — 85,3 ± 6,5%. In the group of non-pregnant women PI was 79,0 ± 5,6%, while, as in the I and the II clinical groups PI was respectively 89,5 ± 5,0% and 94,9 ± 5,3% ($p <0,05$). The APTT was simple test as indicator of activation of coagulation that was sensitive to deficiency of clotting factors and was independent from the platelet count. However, the indicators of APTT in our prospective study, for the first trimester of pregnancy, had no significant difference between the pregnant women with GE and women from the control group. In gestation age of 10–12 weeks, we noted decrease of the APTT till 31,9 ± 3,6 sec among pregnant women from the second clinical group (decidual vasculopathy). The pregnant respondents from I group (non-manifest form of GE) had results of APTT — 34,6 ± 3,0 sec without significant difference compared with normal pregnancy, while among healthy non-pregnant women the result of the APTT was determined as 33,6 ± 2,7 sec.

In the research of platelet haemostasis among women with GE, in the I trimester, was diagnosed decreased platelet count in the second group (203,1 ± 12,6 $x10^9$/L) with significant difference ($p<0,05$) between women with physiological gestation (242,4 ± 12,0 $x10^9$/L). While the platelet count for pregnant women with non-manifest form of GE (the first group) was noted as 215,1 ± 12,8 $x10^9$/L and had significant difference ($p<0,05$) between non-pregnant women — 251,1 ± 10,8 $x10^9$/L only. What is more, in the test for determine of ADP-induced platelet aggregation was showed a significant ($p <0,05$) increase in platelet aggregation in the II clinical group — 47,2 ± 6,2%, relatively among pregnant women with physiological gestation (33,8 ± 3,1%). Interesting was the fact that the performance of platelet aggregation stimulated by ADP (36,1 ± 4,6%) in the first group with GE not differed from the results among pregnant women in the control group. It should be noted that the compared results of platelet haemostasis among pregnant women with clinical manifestation of the GE and non-manifest form of the GE

had enough difference between each other, although without significant difference in the first trimester of pregnancy.

In the study of haemostasis system, we found that the rate of antithrombin III among women with physiological pregnancy in the first trimester was 88,1 ± 6,6%. On the other hand, we can observe that among pregnant women from the I clinical group was noted a slight decrease in antithrombin III till 82,8 ± 8,2%. This trend of change of anticoagulation level haemostasis can be explained violation of the glycosaminoglycan activation of AT-III on the vascular endothelium, that resulting in GE[1]. The other side of the coin is, we was diagnosed a slight increase of AT III, compared to the control group, in the second clinical group (95,1 ± 8,2%) with clinical manifestation of GE in the first trimester. The results may be due to a compensatory stimulation of anticoagulant haemostasis in response to activation of the procoagulant components.

In summary, pregnancy is associated with major changes in haemostasis including increases in the majority of clotting factors, decreases in the quality of natural anticoagulants and a reduction in fibrinolytic activity. Nevertheless, one should accept that, in the first trimester of pregnancy, among women with GE, in general, observed statistically significant changes of the haemostatic parameters only among patients with clinical manifestation. Nevertheless, one should accept that the authentic signs of hypercoagulability at GE, not directly was the trigger factor of the endothelial dysfunction during pregnancy. However, we also agree that our findings were simply results of non-optimal restructuring of vessels in the placental site or complications independent of other causes of the endotheliopathy.

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Protective activity of natural preparation on H7N9 virus

1. Introduction

One of potentially dangerous problems for a human organism is the new strain of a virus of bird flu — A/H7N9. Influenza A (H7N9) belongs to one of subgroups of flu viruses which usually circulate among birds.

Until recently, this virus has not been observed in humans. The first reports of infection with a novel virus group A — the virus H7N9 — appeared in March 2013. Infected people, the people of eastern China and Taiwan, suffered from severe pneumonia and acute respiratory distress syndrome. According to the WHO in May 2013, there have been 132 cases of infection with the new virus, the death toll reached 37.

Therefore, it is obvious that development of natural preparations for strengthening of immune system for improving of protective activity of an organism to arising new viruses is now actual.

One of such preparations is BAE Synergy Liquid (BAE SL) which is representing a water solution of a complex of microelements (silicon, aluminum, magnesium, calcium, iron, manganese, nickel, the titan, chrome, copper, silver, zinc, strontium, sodium, chlorine, sulphate-ion) which with the purpose of giving to one biological activity is activated by a special energetic source.

According to developers stimulates exchange processes and raises physical activity and working capacity of people, and also possesses antimicrobic action in the in vitro experiments[1].

An experiment was conducted to determine the protective activity of the BAE Synergy Liquid preparation to anthrax and influenza A virus (H3N2) on white mice.

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