UDC 618.2: 577.29 **https://doi.org/10.15407/biotech16.02.047**

FIBRINOLYTIC POTENTIAL INCREASING DURING ACTIVATION OF BLOOD COAGULATION IN THE COURSE OF PREGNANCY WITH PLACENTAL DYSFUNCTION

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Received 2023/03/17
Revised 2023/04/26
Accepted 2023/04/28

Hemostasis is an integrative system that supports the blood flow in the vessels and the effective termination of bleeding during trauma. Primary hemostasis, secondary hemostasis and the fibrinolytic system are the three main components of blood coagulation. Pathological activation of blood coagulation can lead to the intravascular thrombus formation. On the other hand, the suppression of blood coagulation can lead to the bleeding disorders. Both thrombosis and hemorrhages are dangerous conditions that can cause severe illness or even death. The dynamic balance in hemostatic system is extremely important during such physiological condition as pregnancy. Any disruption of this balance can be dangerous for mother and for fetus. However, in obstetric clinical practice today especially hypo- and hyper-fibrinolytic disorders are probably underdiagnosed because of lack of knowledge and lack of accurate diagnostic tests [4]. So, the study of molecular mechanisms of hemostasis balance is one of the most vivid tasks for clinical biochemistry.

Aim. In present work we aimed to underline the constant connection between blood coagulation and fibrinolysis.

Methods. Blood samples of women with placental disfunction during pregnancy ($n = 28$) were kindly provided by "Perinatal Center of Kyiv". This study was approved by the Ethics Commission of the Shupyk National Medical Academy of Postgraduate Education and the Ethics Commission of the Kyiv Perinatal Center (# 3 from 05/05/2020).

Blood coagulation activation was estimated by the accumulation of Soluble Fibrin (SF). Highly sensitive and effective immunochemical method for the determination of soluble fibrin by sandwich ELISA was used. As the catch-antibody we used fibrin-specific mAb FnI-3C. As the tag-antibody we used another mAb (II-4d) that has an epitope in the NH 2 -terminal fragment of the γ-chain of the D-region of the fibrin(ogen) molecule. This approach allowed performing quantitative determination in human blood plasma of soluble fibrin that is composed of monomers, dimers and oligomers of fibrin, possibly with fibrinogen molecules at the sticky ends and also initial products of plasmin hydrolysis of fibrin [1, 2].

The rate of activation of fibrinolysis was estimated by measuring of Fibrinolytic Potential (FP). It was measured by turbidimetric method with recording the scattering of light by a fibrin clot at 405 nm on a microplate reader Multiscan (Finland). The clot was formed in the microplate wells in blood plasma activated by APTT reagent in the presence or without t-PA.

The area under the turbidity curve of the clot from the moment of initiation of plasma coagulation to the moment of complete destruction of the clot in the presence of t-PA indicated the Overall hemostasis potential (OHP). Coagulation potential (CP) was the area under the curve of clot formation from the moment of initiation of plasma coagulation to the moment of complete dissolution of the clot in the absence of t-PA. Fibrinolytic potential (FP) was the difference between the values of CP and OHP. As the area under the curves these parameters are being measured in optical units *per* second (ou/s) [3].

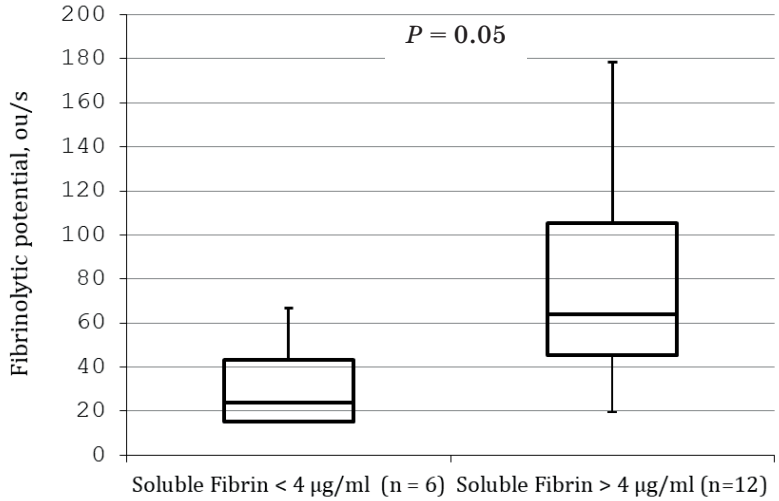

Figure. **Fibrinolytic Potential of blood plasma of pregnant women with placenta dysfunction that had increased vs normal concentration of Soluble Fibrin**

Statistical analysis was performed according to Mann-Whitney U test.

Results. SF was found in blood plasma of 12 pregnant women with placenta dysfunction. Six of studied patients had SF less than 4 μg/ml that were assumed as the control meanings [5]. We divided patients on two groups according to this parameter. It was shown that patients of the 1st group (SF ≤ 4) exhibited FP as 24 ou/s. In the same time patients of the 2nd group (SF ≥ 4) had much higher FP — 62 ou/s. The level of statistical significance was $P = 0.05$.

Discussion. In normal pregnancy, there is a marked increase in the procoagulant activity in maternal blood characterized by elevation of factors VII, X, VIII, fibrinogen and von Willebrand factor, which is maximal around term. This is associated with an increase in prothrombin fragments (PF1+2) and thrombin–antithrombin complexes [6]. Changes in the hemostasis system under the conditions of pregnancy with pathologies remains an actual topic and requires research. Some studies demonstrate that disorders during pregnancy (for example, preeclampsia) are characterized by changes in the t-PA/PAI-1 system indicating an endothelial dysfunction [7]. Our study revealed an interesting interrelation between FP and SF (more SF — higher FP) in the blood system of pregnant women with placental dysfunction. We assume that this is the sign of mutual regulation between coagulation and fibrinolysis in hemostasis. In our opinion, the activation of blood coagulation system (which can be estimated by the accumulation of SF) leads to the activation of fibrinolysis. Such compensatory activation is needed for effective dissolution of any clot that can appear in the bloodstream. It is unclear if the SF as the oligomers of fibrin can stimulate fibrinolysis directly, or some other mechanisms of interconnection are involved. The introduction of a complex indicator into laboratory practice, taking into account CP and FP, will allow more adequately assessing the presence of a thrombophilic state in patients with vascular-placental disorders and preventing the development of such complications.

Conclusions. Blood coagulation activation (estimated by SF measurement) was shown to be accompanied by fibrinolysis activity increasing (measured by FP evaluation) in pregnant women with placental dysfunctions. These findings can be evidence of constant balance between blood coagulation and fibrinolysis that stabilize hemostasis in pathological conditions for avoiding thrombosis or hemorrhages.

Keywords: soluble fibrin; pregnancy; fibrinolysis; fibrinolytic potential; blood coagulation.

Ethical Committee Approval: # 3 from 05/05/2020

Acknowledgement. Authors gratefully acknowledge Prof. S. I. Zhuk and Dr. V. O. Chernyshenko for their contribution to this work.

Author's contribution. Y. Tsaryk performed soluble fibrin and overall hemostatic potential measuring, I. Us supervised and monitored the patients.

Funding. The research was financed by the project No. 0119U002512 "The interaction of the hemostasis system components at the cellular and molecular level in the process of formation and elimination of a thrombus".

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