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CHARACTERISTICS OF MARKERS OF ENDOTHELIAL DYSFUNCTION IN THE BLOOD OF WOMEN WITH PRETERM BIRTH

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Таянч сўзлар: endotelial disfunktsiya, erta tug'ilish, homiladorlik.
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Key words: endotelial disfunktsiya, muddatdan oldingi tuq'ruq, homiladorlik.

Recently, vascular and hemodynamic disorders in the mother, which are observed in various somatic diseases, have traditionally been attributed to risk factors for preterm birth. At the heart of violations of hemodynamics and microcirculation, including in the uteroplacental pool, developing with preeclampsia and various somatic pathologies, is a generalized dysfunction of the endothelium. It is extremely important to study the content in the blood of pregnant women with premature birth of indicators of the anticoagulant potential of the blood, in particular, the content of the main anticoagulant, antithrombin III. In preterm birth, its amount was 85.15 ± 5.31 mg/l, which is significantly lower than in women with a physiological course of pregnancy, which indicates the important role of antithrombin III deficiency in the development of these severe pregnancy complications.

MUDDATIDAN OLDIN TUG'GAN AYOLLAR QONIDA ENDOTELIAL DISFUNKSIYON MARKERLARINING XUSUSIYATLARI

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So'nggi paytlarda turli somatik kasalliklarda kuzatiladigan onadagi qon tomir va gemodinamik buzilishlar an'anaviy ravishda erta tug'ruqning xavf omillari bilan bog'liq. Gemodinamika va mikrosirkulyatsiyaning buzilishi, shu jumladan fetoplasentar tizimda, preeklampsiya va turli somatik patologiyalar bilan rivojlanayotgan endoteliyning umumiy disfunktsiyasi asosida kechadi. Muddatidan oldin tug'gan homilador ayollarning qon tarkibidagi antikoagulyant potentsial ko'rsatkichlarini, xususan, asosiy antikoagulyant - antitrombin III ning tarkibini o'rganish juda muhimdir. Erta tug'ruqda uning miqdori 85,15 ± 5,31 mg / l ni tashkil etdi, bu homiladorlikning fiziologik kechishi bo'lgan ayollarga qaraganda sezilarli darajada past bo'lib, bu homiladorlikning ushbu og'ir asoratlarini rivojlanishida antitrombin III etishmovchiligining muhim o'rnini ko'rsatadi.

ХАРАКТЕРИСТИКА МАРКЕРОВ ДИСФУНКЦИИ ЭНДОТЕЛИЯ В КРОВИ У ЖЕНЩИН С ПРЕЖДЕВРЕМЕННЫМИ РОДАМИ

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В последнее время к факторам риска преждевременных родов традиционно относят сосудистые и гемодинамические нарушения у матери, которые наблюдаются при различных соматических заболеваниях. В основе нарушения гемодинамики и микроциркуляции, в том числе в маточно-плацентарном бассейне, развивающихся при гестозе и различной соматической патологии, лежит генерализованная дисфункция эндотелия. Чрезвычайно важным является изучение содержания в крови беременных женщин с преждевременными родами показателей антикоагуляционного потенциала крови, в частности, содержания основного антикоагулянта — антитромбина III. При преждевременных родах его количество составило 85,15±5,31 мг/л, что достоверно ниже, чем у женщин с физиологическим течением беременности, что свидетельствует о важной роль дефицита антитромбина III в развитии этих грозных осложнений беременности.

Relevance of the problem: There are several hypotheses that explain the development of endothelial dysfunction in the pathological course of pregnancy [6,7,8]. The theory of placental ischemia received the greatest evidence. Absolute or relative placental ischemia may develop primarily as a result of insufficient invasion of the trophoblast into the spiral arteries of the decidua, or secondarily as a result of diffuse endothelial pathology observed in patients with somatic pathology. As a result of placental ischemia, endothelial-damaging substances enter the bloodstream, an imbalance occurs between vasoconstrictors and vasodilators, between the thrombogenic potential of the vascular wall and its thromboresistance, regional blood flow is disturbed, and progressive disorders of vital organs and functions of the placenta occur [9,10]. Additional methods for diagnosing preterm birth include the determination of fetal hemoglobin in maternal blood, but this method is not sensitive and specific enough. An important indicator is the determination of PDfn

and PDfg as markers of intravascular consumption of blood coagulation factors in this pathology [11]. In preterm birth, thromboplastic substances of tissue and cellular origin enter the maternal circulation, resulting in hyperthrombinemia and intravascular coagulation. Plasma fibronectin (PFN) is one of the substances with opsonizing ability, due to which it largely determines and regulates phagocytic activity in normal conditions and stimulates this process during inflammation. By now, it is well known that PFN is able to bind and eliminate products of phagocytosis (particles of tissue detritus, endotoxins of viruses and bacteria), as well as immune complexes through the macrophage system, as well as immune complexes [2]. It acts as a kind of marker of the acute phase of inflammation. A decrease in the level of plasma fibronectin in plasma is observed: with hepatitis, with sepsis, with physical injuries, in the postoperative period.

The concentration of plasma fibronectin in plasma increases: during complicated pregnancy (severe preeclampsia, preeclampsia), in violation of the vascular endothelium, in inflammation, in the development of malignant tumors and their metastasis.

The purpose of this study was: to study the diagnostic value of determining in the blood a number of markers of the functional state of the endothelium in women with preterm labor.

Material and methods of research: 72 patients were examined. The main group consisted of 48 full-term pregnant women with premature birth in the absence of biological readiness for childbirth. The inclusion criterion was preterm birth, gestational age of 28-36 weeks, insufficient readiness of the soft birth canal for labor induction (w/uterus: immature, maturing), lack of indications for emergency delivery. Exclusion criteria: signs of ascending infection (leukocytosis, body temperature), diabetes mellitus, uterine scar, large fetus, breech presentation of the fetus, chronic urogenital infection with a history of complications (miscarriage, premature birth, endometritis, acute adnexitis). In the examined patients, active-watchful tactics were used up to 72 hours of the anhydrous period. A comprehensive examination of the condition of the pregnant woman and the fetus was carried out. At 12 hours of the anhydrous period, antibiotic therapy was started to prevent ascending infection. Preparation for childbirth was carried out with antispasmodics, antioxidants, antigestagens. Miropriston was prescribed after premature rupture of amniotic fluid at a dose of 0.2 g twice. The first time - immediately after the discharge of amniotic fluid. The second - after 6 hours, in the absence of regular labor activity. Upon reaching the optimal biological readiness for childbirth or the appearance of signs of an ascending infection, labor induction was performed. The control group included 24 patients of the same period with timely discharge of amniotic fluid without severe obstetric and somatic pathology of PIOV in the absence of biological readiness for childbirth.

To achieve this goal, a blood test was carried out for the content of markers of endothelial dysfunction: thrombomodulin, soluble adhesion molecules (sICAM-1 and sVCAM-1), von Willebrand factor, fibronectin.

Blood for the study was taken from the cubital vein into a plastic or siliconized test tube containing a 3.8% solution of sodium citrate 3-substituted (sodium citrate), the ratio of blood volumes to sodium citrate was 9:1. Blood was centrifuged at 3000–4000 rpm (1200 g) for 15 minutes. As a result, platelet-poor plasma was obtained, which was transferred to another tube, where it was stored until the study. Plasma with clots, hemolysis, excess sodium citrate and obtained more than 2 hours ago was not allowed to be analyzed. Frozen plasma samples were stored at -20 to -16°C for no more than 1 month.

The blood levels of sVCAM-1, sICAM-1, and thrombomodulin were determined using human sVCAM ELISA, human sICAM ELISA, and human sCD141 ELISA reagents manufactured by Diaclon (France). To determine fibronectin, avntitrombin-III, the IFA-Fn kit manufactured by CJSC NVO Immunoteks was used. To determine the deficiency of proteins C, the set "Sail-test" manufactured by "Technology-Standard" was used. Specific semiquantitative determination in plasma of fibrin cross derivatives containing the D-dimer domain was carried out by latex agglutination immunoassay.

Statistical processing of the material was performed using the standard statistical software

package Statistica 10.0 (Statistica for Windows v. 6.0).

Results of the study and their discussion: One of the most important methods for diagnosing endothelial dysfunction is the assessment of the blood levels of various substances formed in the endothelium. Not all indicators have the same diagnostic value, since a significant part of the markers of the functional state of the endothelium, in addition to endotheliocytes, are also formed in other cells. Highly specific markers of endothelial dysfunction include thrombomodulin and soluble adhesion molecules, ICAM-1 and VCAM-1. Thrombomodulin is a glycoprotein in the endothelial membrane and a cellular receptor for thrombin. It converts protein C into its active form, performing an anticoagulant function. The content of thrombo-bomodulin in the blood increases with damage to the endothelium.

The adhesion molecules, ICAM-1 and VCAM-1, belong to the immunoglobulin superfamily and bind to leukocyte membrane integrins. They are expressed by endotheliocytes and partially pass into the blood upon activation of the endothelium. An increase in the content of soluble adhesion molecules in the blood is a highly specific marker of endothelial dysfunction. Increased adhesiveness of the endothelium is of great importance in the pathogenesis of atherosclerosis, systemic inflammatory response syndrome and other pathological conditions. A highly specific marker of the functional state of the endothelium is also the von Willebrand factor, which promotes platelet adhesion to the damaged endothelium. Platelets are another source of von Willebrand factor. Fibronectin is a subendothelial extracellular glycoprotein that is also found in platelets and plasma and is an important platelet adhesion factor at the site of vascular injury. Unlike the above markers, fibronectin is not a strictly specific marker of endothelial dysfunction, since it is synthesized not only by endotheliocytes, but its content in the blood increases in pathology accompanied by damage to the vascular wall. So, X. Wang et al. fibronectin was determined at 24–34 weeks. In those women who developed subsequent IUGR, fibronectin levels were significantly higher. Our studies presented in Table 1 show that an elevated level of plasma fibronectin in the control group occurs in 13% of cases, while in the PIOV group it is increased in 25% of cases.

Important for understanding the role of endothelial dysfunction in the pathogenesis of PIOV is the study of the dynamics of markers of endothelial dysfunction. As can be seen from Table. 1, the content of endothelial dysfunction markers, such as thrombomodulin, soluble adhesion molecules, von Willebrand factor and fibronectin, had a peculiar dynamics in PIOV. The results of our study showed an increase in the content of thrombomodulin, sICAM-1, von Willebrand factor, fibronectin in the maternal bloodstream during preterm birth, which indicates the activation and stimulation of endotheliocytes in this pathology. In women with preterm birth, a statistically significant increase in the content of fibronectin in the blood was observed, which appears to be associated with damage to the trophoblast. The source of the increase in the content of thrombomodulin in the blood of these women also seems to be the trophoblast. As you know, as the gestational age increases, the degree of thrombinemia increases, which is detected by an increase in the content of soluble fibrin-monomer complexes (SFMK), fibrinogen degradation products (PDF) and fibrin (D-dimer). These changes are associated with the intensification of the processes of intravascular blood coagulation, including in the uteroplacental blood flow. To date, the most accessible, often performed in domestic laboratories and quite informative is the D-dimer test. During pregnancy, due to an increase in the total coagulation potential of the blood, a thrombophilic condition almost always develops. Such changes in the hemostasis system during physiological pregnancy are considered necessary for the normal formation of the fetoplacental complex. Their development is associated with such morphological and functional changes in the spiral arteries of the uterine mucosa, such as invasion of trophoblast cells into the arterial wall, replacement of the internal elastic membrane and internal media with a thick layer of fibrinoid, violation of the integrity of the endothelium and exposure of collagen structures, as well as the formation intervillous space. Developing changes, as a rule, are not accompanied by pathological hyperthrombinemia and disseminated intravascular blood coagulation (DIC), however, they can lead to hypercoagulability, which is the result of an imbalance in the hemostasis system under conditions of hereditary and/or

acquired shifts in various extragenital diseases. Thrombophilic status can lead to disruption of adaptive mechanisms during pregnancy and childbirth and cause the development of obstetric complications - growth retardation and fetal development, placental insufficiency, late toxicosis (preeclampsia), fetal death, etc. The severity of changes in the vascular and platelet , coagulation, fibrinolytic and anticoagulant links of hemostasis is determined by the characteristics of the course of pregnancy and the initial state of the coagulation system. These factors are interrelated and interdependent; their violations often lead to termination of pregnancy at different times, which makes timely diagnosis of intravascular thrombosis and its therapy using specific and non-specific methods that affect individual links of pathogenesis relevant. It is extremely important to study the content in the blood of pregnant women with premature birth of indicators of the anticoagulant potential of the blood, in particular, the content of the main anticoagulant, antithrombin III. In preterm birth, its amount was 85.15 ± 5.31 mg/l, which is significantly lower than in women with a physiological course of pregnancy, which indicates the important role of antithrombin III deficiency in the development of these severe pregnancy complications.

Table 1.

Frequency of occurrence of general and local symptoms in the examined patients upon admission

Group surveyed	Indicator				
	Thrombomodulin	ng/ml Factor	Willebrand	sICAM-1 ng/ml	sVCAM-1 ng/ml
Physiological flow pregnancy (n=12)	6.76 ± 0.38	109.45 ±5.07	233.14 ±9.67	998.92±14.6	742.34±9.78
pregnant with risk for PB n=72	8.96 ± 0.53	169.45 ±6.37	503.23 ±10.24	1308.92±51.6	797.51±12.45

*Note: *-significance of differences P < 0.05*

Considering that the coagulation potential according to the APTT, PT and RFMK tests in women with preterm labor tended to increase, it can be assumed that the decrease in antithrombin activity in our studies is associated with the depletion of the anticoagulant system and may be the cause of the development of gross shifts in the hemostasis system.

Table 2.

The content of markers of endothelial dysfunction in the blood of pregnant women with premature birth

Group	Protein C %	D-dimer	Antithrombin ng/ml
surveyed	84.76 ± 6.38	179.23 ±9.07	109.45 ±7.33
Physiological course	128.58 ± 9.53	317.45 ±10.37*	85.15 ±5.31*

*Note: *-significance of differences P < 0.05*

We also screened disorders in the protein C system in pregnant women with preterm labor, which revealed a statistically significant increase in the amount of protein C in the blood. Therefore, with premature rupture of amniotic fluid, a decrease in the content of antithrombin III is detected, against the background of an increase in the level of protein C, due to high values of thrombomodulin. In order to identify the activation of intravascular coagulation in women with premature rupture of amniotic fluid, the content of D-dimer in the blood was examined. In 49.8% of women with premature rupture of amniotic fluid, an increase in the content of D-dimer in the blood above 300 ng/ml was revealed. This indicates the processes of fibrin cross-polymerization in the process of intravascular blood coagulation, which is observed at the time of the developed clinical picture of premature rupture of amniotic fluid. Consequently, in preterm birth, there is a deficiency of natural anticoagulants (antithrombin III) and activation of intravascular coagulation (an increase in the content of protein C and D-dimer). It is possible that the presence of congenital defects in the hemostasis system, which create an unfavorable premorbid background and contribute to the manifestation of hypercoagulability in the intervillous space, can serve as an important path-

ogenetic factor in preterm birth.

Thus, on the basis of the obtained research results, it can be indicated that the detection of an increase in the blood content of D-dimer, protein C, antithrombin III has the highest specificity, positive and negative predictive value, and diagnostic accuracy, and the highest sensitivity is an increase in the content of thrombomodulin.

Therefore, the determination of blood levels of a number of markers of endothelial dysfunction, such as thrombomodulin and fibronectin, as well as a marker of intravascular blood coagulation D-dimer, protein C, is diagnostically and prognostically significant in the diagnosis of premature rupture of amniotic fluid in pregnant women.

References:

1. Л. В. Саркисова Иммунологические аспекты при преждевременных родах // Вестник врача, № 2 (99), 2021. С.171-176. DOI: 10.38095/2181-466X-2021992-171-176
2. Л. В. Саркисова, Г. М. Каюмова, Д. У. Рузиева Современные тренды преждевременных родов // Вестник врача, № 4, 2019. С.109-113.
3. Л. В. Саркисова, Д. Э. Насретдинова Взаимосвязь биохимических и гемодинамических показателей при преждевременных родах // Вестник врача, № 2 (99), 2021. С.89-94. DOI: 10.38095/2181-466X-2021992-89-94
4. Г. Ю. Тураева Преждевременные роды: частота, причины и последствия // Вестник врача, № 3 (95), 2020. С.94-97. DOI: 10.38095/2181-466X-2020953-94-97
5. Г. Ю. Тураева Состояние гемодинамических и морфологических параллелей у женщин с преждевременными родами в анамнезе // Вестник врача, № 1 (93), 2020. С.80-82. DOI: 10.38095/2181-466X-2020931-80-82
6. Н. Н. Шавази Профилактика преждевременных родов, современная диагностика и медикаментозная терапия // Вестник врача, № 3, 2019. С.122-124.
7. Alexander, J. Thomas PW, Sanghera J. Treatments for secondary postpartum haemorrhage // Cochrane Database of Systematic Reviews. - 2002. -Issue 1. - Art. №: CD002867. DOI: 10.1002/14651858.CD002867.
8. Arulpragasam, K. Emergency peripartum hysterectomy in a Western Australian population: Ten-year retrospective case-note analysis. AUST NZ J OBSTET GIN/K. Arulpragasam, G. Hyanes, M. Epee-Bekima // Obstet Gynaecol. -2018. - Nov., № 8. - P 456-469. doi: 10.1111/ajo.12922 [Epub ahead of print].
9. Bonnet, M.-P. Postpartum Haemorrhage in Canada and France: A Population-Based / M.-P. Bonnet, O. Basso, M.-H. Bouvier-Colle [et al.] // Comparison. PLoS ONE.-2013. - № 8(6).-P.66-88. doi:10.1371/journal.pone. 0066882.
10. Burgos Frías N. Iliac artery occlusion balloons for suspected placenta accreta during cesarean section. Article in Spanish / N. Frías Burgos, E. Gredilla, E. Guasch [et al.] // Rev. Esp. Anestesiol Reanim. - 2014. - № 61(2). - P. 105-8. doi: 10.1016/j.redar.2012.11.008. Epub 2012 Dec 29.
11. Butwick, A. J. Risk factors for obstetric morbidity in patients with uterine atony undergoing caesarean delivery / A. J. Butwick, B. Carvalho, Y. Y. El-Sayed // Br. J. Anaesth. - 2014. - № 113(4). - P. 661-8. doi: 10.1093/bja/aeu150. Epub 2014 Jun 6.
12. Butwick, A. J. Second-line uterotonics and the risk of hemorrhage-related morbidity / A. J. Butwick, B. Carvalho, Y. J. Blumenfeld [et al.] // Am. J. Obstet Gynecol. - 2015. - № 212(5). - P. 642-7. doi: 10.1016/j.ajog.2015.01.008. Epub 2015 Jan 9.
13. Chandraharan, E. The Triple-P procedure as a conservative surgical alternative to peripartum hysterectomy for placenta percreta / E. Chandraharan, S. Rao, A. M. Belli [et al.] // Int. J. Gynaecol Obstet. - 2012. - № 117(2). -P. 191- 4. doi: 10.1016/j.ijgo.2011.12.005. Epub 2012 Feb 11.
14. Choi, S. R. Is a cause of postpartum hemorrhage of using of tocolytic agents in preterm delivery? / S. R. Choi, N. R. Yoon, S. O. Hwang // J. Matern Fetal Neonatal Med. - 2017. - № 30(22). - P. 2711-2715. doi: 10.1080/14767058.2016.1261397. Epub 2016 Dec 7.
15. Claroni, C. Postpartum hemorrhage management, the importance of timing / C. Claroni, M. Aversano, C. Todde [et al.] // Clinical Management. -2018. - P. 12. doi: https://doi.org/10.7175/cmi.v12i1.1326.
16. Dahlke, J. D. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines / J. D. Dahlke, H. Mendez-Figueroa, L. Maggio [et al.] // Am. J. Obstet Gynecol. - 2015. - № 213(1). - P. 76.-10. doi: 10.1016/j.ajog.2015.02.023. Epub 2015 Feb 28.
17. D'Antonio, F. (2016), Counseling in fetal medicine: evidence-based answers to clinical questions on morbidly adherent placenta / F. D'Antonio, J. Palacios-Jaraquemada, P. S. Lim [et al.] // Ultrasound Obstet Gynecol. - 2016. -№ 47. - P. 290-301. doi: 10.1002/uog.14950.
18. De Visser, S. M. Development of a tailored strategy to improve postpartum hemorrhage guideline adherence / S.

M. De Visser, M. D. Woiski, R. P. Grol [et al.] // BMC Pregnancy and Childbirth. - 2018. - № 18. - P. 49. -doi: http://doi.org/10.1186/s12884-018-1676-6.
19. Ekelund, K. Hemostatic resuscitation in postpartum hemorrhage -a supplement to surgery / K. Ekelund, G. Hanke, J. Stensballe [et al.] // Acta Obstet Gynecol Scand. - 2015. - № 94(7). - P. 680-692. doi: 10.1111/aogs.12607. Epub 2015 Mar 5.
20. Eshkoli, T. Placenta accreta: risk factors, perinatal outcomes, and consequences for subsequent births / T. Eshkoli, A. Y. Weintraub, R. Sergienko [et al.] // Am. J. Obstet Gynecol. - 2013. - № 208(3). - P. 219.-7. doi: 10.1016/ j.ajog.2012.12.037. Epub 2013 Jan 8.
21. Evensen, A. Postpartum Hemorrhage: Prevention and Treatment / A. Evensen, J. M. Anderson, P. Fontaine // Am. Fam. Physician. - 2017. -№ 1; 95(7). - P. 442-449.
22. Fadel, M. G. Maternal outcomes following massive obstetric haemorrhage in an inner-city maternity unit / M. G. Fadel, S. Das, A. Nesbitt [et al.] // J. Obstet Gynaecol. - 2019. - Mar., № 1. - P. 1-5. doi: 10.1080/01443615.2018.1534814 [Epub ahead of print].
23. Ford, J. B. Trends and outcomes of postpartum haemorrhage, 20032011 / B. J. Ford, J. A. Patterson, K. M. Sean Seeho [et al.] // BMC Pregnancy and Childbirth. - 2015. - № 15. - P. 334. doi: https://doi.org/10.1186/s12884-015-0788-5.
24. Gallos, I. D. Uterotonic agents for preventing postpartumhaemorrhage: a networkmeta-analysis / I. D. Gallos, H. M. Williams, M. J. Price [et al.] // Cochrane Database of Systematic Reviews. - 2018. - Issue 4. -Art. №: CD011689. DOI: 10.1002/14651858.CD011689.pub2.
25. Guasch, E. Massive obstetric hemorrhage: Current approach to management. Article in English, Spanish / E. Guasch, F. Gilsanz // Med. Intensiva. - 2016. - № 40(5). - P. 298-310. doi: 10.1016/j.medin.2016.02.010. Epub 2016 May 13.
26. Guasch, E. Hemorragia masiva obstétrica: enfoque terapéutico actual / E. Guasch, F. Gilsanz // Med. Intensiva. - 2016. - № 40. - P. 298-310.
27. Guida, J. P. Brazilian Cohort on Severe Maternal Morbidity (COMMAG) study group and the WHO Maternal Morbidity Working Group (MMWG). The impact of hypertension, hemorrhage, and other maternal morbidities on functioning in the postpartum period as assessed by the WHODAS 2.0 36-item tool / J. P. Guida, M. L. Costa, M. A. Parpinelli [et al.] // Int. J. Gynaecol Obstet. - 2018. - № 141. - Suppl 1. - P. 55-60. doi: 10.1002/ijgo.12467.
28. Guideline on the Management of Postpartum Haemorrhage, HSE Home Birth Service. - Dublin, Ireland. 2018. - URL : https://www.hse.ie/eng/services/list/3/maternity/hb010-pph-guideline-hse-home-birth-service-2018.pdf
29. Harvey, C. J. Evidence-Based Strategies for Maternal Stabilization and Rescue in Obstetric Hemorrhage / C. J. Harevey // AACN Adv Crit Care. - 2018. -№ 29(3). - P. 284-294. doi: 10.4037/aacnacc2018966.
30. Henriquez, D. D. C. A. Management of postpartum hemorrhage: how to improve maternal outcomes? / D. D. C. A. Henriquez, K. W. M. Bloemenkamp,
31. J. G. van der Bom // Journal of Thrombosis and Haemostasis. - 2018. -№ 16 (8). - P. 1523-1534. DOI: 10.1111/jth. 14200.