

Schemes for Diagnosing Hemostatic Disorders during a Complicated Pregnancy

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ABSTRACT

Considering the previously presented data on the dynamics of hemostatic and fibrinolytic characteristics during a normal pregnancy, we propose schemes for diagnosing hemostatic disorders in pregnant women at risk of gestational and thromboembolic complications and obstetric hemorrhages.

Key words: Hemostatic; Fibrinolytic; Obstetric hemorrhages; Thromboembolic complications

INTRODUCTION

At present, the schemes for testing hemostatic system, both during normal and complicated pregnancies, are not systematized. On the one hand, this is due to the lack of consistent data between specialists on the acceptable values of hemostatic characteristics in different pregnancy periods and, on the other hand, due to different views on hemostatic characteristics that must be considered during gestation.

Previously, interim results of a pilot single-center cohort study of hemostatic system in a normal pregnancy in a Russian female population were published [1]. In 2018, the study was completed and the working group presented the acceptable values of hemostatic reactions, which explain the most likely causes of blood coagulation disorders and are most probable to deviate in a complicated pregnancy [2]. In the space of 8 years (2010-2017), 521 women were examined by employees of the Altai branch of the National Medical Research Center of Hematology on more than 70 hemostatic characteristics at different periods of a normal pregnancy. The tests were performed at nine time points that consider trophoblast invasion waves and reflect “critical” periods of a normal pregnancy and the preconceptional period: 7–8 weeks, 12–13 weeks, 18–19 weeks, 22–23 weeks, 27–28 weeks, 32–33 weeks, 36–37 weeks and 2–3 days after delivery.

Based on hemostatic reaction behavior in a normal pregnancy, it is possible to estimate the direction of hemostatic changes in pregnant women at risk of hemorrhagic, thromboembolic or gestational complications.

MATERIALS AND METHODS

The study was aimed at defining the minimal but sufficiently informative number of laboratory tests in groups at risk of pregnancy complications.

In accordance with the authors’ opinion, as well as on the basis of guidance from leading international scientific medical organizations (American College of Chest Physicians, European and Mediterranean League Against Thrombotic Diseases, International Federation of Obstetrics and Gynecologists, International Society on Thrombosis and Haemostasis, the Japanese Society on Thrombosis and Hemostasis) and articles in PubMed, Medline and LIBRARY.RU databases, diagnostic schemes for the following risk groups are defined:

- Obstetric coagulopathic bleeding
- Pre-eclampsia
- Venous thromboembolic complications (VTECs)
- Antiphospholipid syndrome (APS)
- Life-threatening conditions.

Scheme for examining patients at risk of coagulopathic bleeding

- Clinical criteria for inclusion in the risk group: a congenital bleeding diathesis (von Willebrand disease, thrombocytopathia), characterized by the onset since childhood, microvascular bleeding (nasal bleeding, gingival bleeding, easy bruising, hyperpolymenorrhea, bleeding after minor surgery - tooth extraction, tonsillectomy).

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- Recommended time points and tests are presented in Table 1 [3-17].

Scheme for examining patients at risk of pre-eclampsia

- Clinical criteria for inclusion in the risk group: early onset pre-eclampsia and preterm delivery <34 weeks in history; preeclampsia in more than one previous pregnancy; chronic kidney disease; autoimmune diseases: systemic lupus erythematosus, antiphospholipid syndrome; hereditary thrombophilia (FVL G1691A mutation, prothrombin G20210A mutation, severe antithrombin III, protein C or protein S deficiency); diabetes mellitus type 1 or 2; chronic hypertension; body mass index of 35 kg/m² or more at the first visit.
- Recommended time points and tests are presented in Table 2 [3,9-21].

Scheme for examining patients at risk of venous thromboembolic complications (VTECs)

- Clinical criteria for inclusion in the risk group: recurrent thrombosis, both not provoked and associated with estrogen-containing drugs; family thrombotic history (VTECs in first-degree relatives younger than 50 years); artificial heart valves, cava filter; severe preeclampsia and fetal death during that pregnancy; thrombophilic genotypes: hetero-and homozygous factor V Leiden (FVL G1691A) mutation, homozygous prothrombin G20210A mutation, antithrombin III (AT III), protein S and C deficiency; extragenital pathology (malignant diseases, diabetes mellitus type 1, nephrotic syndrome, SLE, sickle cell anemia).
- Recommended time points and methods for hemostatic system testing are presented in Tables 2 and 3 [22-34].

Scheme for examining patients at risk of antiphospholipid syndrome (APS)

Clinical criteria for inclusion in the risk group [26,35]:

Table 1: Recommended time points and methods for hemostatic system testing in patients at risk of obstetric coagulopathic bleeding [3-17].

Test	Time points			
	PC	7-8 weeks	27-28 weeks	36-37 weeks
Platelet count	+	+	+	+
ADP-induced platelet activation (2.0 µmol/L)	+	+	-	-
von Willebrand factor	+	+	-	-
APTT	+	+	-	+
PT	+	+	-	+
Fibrinogen	+	+	-	+
Factor XIII (fibrin-stabilizing)	-	-	-	+
Thromboelastography	-	-	-	+

PC: Preconceptional Period

*Absence of data when planning for pregnancy.

Table 2: Recommended time points and methods for hemostatic system testing in patients at risk of preeclampsia [3,19-21].

Test	Time points			
	PC	7-8 weeks	27-28 weeks	36-37 weeks
Platelet count	+	+	+	+
APTT	+	+	-	+
Prothrombin time	+	+	-	+
Fibrinogen	+	+	-	+
Homocystein	+	-	-	-

PC: Preconceptional Period

Table 3: Recommended time points and methods for hemostatic system testing in patients at risk of VTECs [22-34].

Test	Time points				
	PC	7-8 weeks	18-19 weeks	27-28 weeks	36-37 weeks
Platelet count	+	+	+	+	+
ADP-induced platelet activation (0.1 µmol)	+	+	+	-	-
APTT	+	+	-	-	+
Prothrombin time	+	+	**	**	+
Fibrinogen	+	+	-	-	+
D-dimer	-	+	-	+	+
Antithrombin III	+	+	-	-	+
Screening for protein C disorders	+	+	-	-	+
Activated protein C resistance	+	+	-	-	+

PC: Preconceptional Period

*Absence of data when planning for pregnancy

**Testing is performed during vitamin K antagonist treatment

- Vascular thrombosis: one or more clinical episodes of arterial, venous thrombosis or thrombosis of small vessels in any tissue or organ. Thrombosis must be confirmed by either medical imaging, Doppler ultrasonography or morphologically, with the exception of superficial venous thrombosis. Morphological confirmation should not have a significant inflammation of the vascular wall.
- Pregnancy disorder: a) one or more episodes of intrauterine death of a morphologically normal fetus after 10 weeks of gestation (normal morphological fetus signs were documented by an ultrasound or fetoscopy) or b) one or more episodes of preterm delivery of a morphologically normal fetus before 34 weeks of gestation due to severe pre-eclampsia or eclampsia, or severe placental insufficiency, or c) three or more consecutive episodes of spontaneous abortion till 10 weeks of gestation (exceptions: anatomical uterine defects, hormonal disorders, maternal or paternal chromosomal abnormalities).
- APS diagnostic criteria: one clinical and one laboratory criteria is needed (in any combination).
- The recommended time points and methods for hemostatic system testing are presented in Table 4 [26,35-42].

Scheme for examining patients at risk of life-threatening conditions caused by pregnancy

- The leading critical conditions that determine maternal mortality include disseminated intravascular coagulation syndrome (DIC) and various clinical forms of thrombotic microangiopathy (TMA), which are based on damage to the vascular endothelium of the microcirculatory bed, caused by disseminated thrombus formation [43,44]. During gestation, the clinical variants of TMA include several diseases: atypical hemolytic-uremic syndrome (aHUS), thrombotic thrombocytopenic purpura (TTP), pre-

eclampsia/eclampsia, HELLP-syndrome and catastrophic antiphospholipid syndrome (CAPS) [45-49].

Clinical criteria for inclusion in the risk group:

- Risk of DIC: Acute massive blood loss; amniotic fluid embolism; premature detachment of the normally situated placenta; intrauterine fetal death; chorioamnionitis;
- TMA clinically manifested as: organ dysfunction of various localization; thrombocytopenia combined with hemolytic anemia; schizocytosis; increased activity of hepatic transaminases (ALT, AST); increased LDH level.

The recommended scheme of hemostatic system testing for life-threatening conditions is presented in Table 5 [50-112].

To define patient management, the primary task is the differential diagnosis between DIC, secondary and primary TMA forms (pre-eclampsia, HELLP syndrome and CAPS): atypical hemolytic-uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) [55,63,112]. One of the major criteria for TMA diagnosis is ADAMTS-13 metalloproteinase activity [55]. For a hereditary form of thrombotic thrombocytopenic purpura, ADAMTS-13 deficiency is typical (activity less than 5-10%) [18,107]. Atypical hemolytic-uremic syndrome is characterized not only by a decrease in the activity of ADAMTS-13 metalloproteinase, but also by antibodies to it [47].

Table 6 shows the dynamics of laboratory characteristics, based on the articles listed in Table 5.

RESULTS AND DISCUSSION

The presented data are expert opinions based on many years' experience of the specialists in the Altai branch of FSBI "National Research Center for Hematology" as well as on a number of

Table 4: Recommended time points and methods for hemostatic system testing in patients at risk of APS [26,35-42].

Test	Time points				
	PC	7-8 weeks	17-18 weeks	27-28 weeks	36-37 weeks
Platelet count	+	+	+	+	+
APTT	+	+	-	-	+
Prothrombin time	+	+	-	-	+
Fibrinogen	+	+	-	-	+
Lupus anticoagulant*	+	+	+	+	+
IgG and/or IgM antibodies to cardiolipin *	+	+	+	+	+
IgG and/or IgM antibodies to b2-glycoprotein	+	+	+	+	+

*If lupus anticoagulant is found in plasma 2 or more times with an interval of at least 12 weeks or antibodies are found in serum or plasma with titer >99th percentile at least 2 times with an interval of at least 12 weeks

Test	Reference articles
Platelet count	[3,50-69]
ADAMTS-13 metalloproteinase	[5,70-76]
PT	[77-87]
Fibrinogen	[77,81-84, 88-91]
Thromboelastography	[9,10,12,30,92]
D-dimer	[26,81, 93-97]
Antithrombin III	[22,23,28,98,99-102]
Lupus anticoagulant	[103-106,108-111]

Table 5: The recommended scheme of hemostatic system testing in patients at risk of life-threatening conditions.

Table 6: Diagnostic criteria for life-threatening conditions.

Test	DIC	CAPS	Obstetric TMA (severe preeclampsia, HELLP syndrome)	aHUS	TTP
Platelet count	↓	↓	↓	↓	↓↓
ADAMTS-13 metalloproteinase	↓	↓	↓	↓	↓↓
PT	↑	N/↑	↑	N	N
Fibrinogen	↓	N	N/↓	N	N
D-dimer	↑	↑	↑	N	N
Antithrombin III	↓	N/↓	↓	N	N
Lupus anticoagulant	N	↑	N	N	N
Thromboelastography	Hypercoagulation/ hypocoagulation/ Hypofibrinolysis/ hyperfibrinolysis*	Normal/hypercoagulation	Hypocoagulation	Clot density decrease	

↑: Moderate increase; ↓: Moderate decrease; ↓↓: A significant decrease; N: Within reference values
*Depending on DIC clinical phenotype (thrombotic or fibrinolytic)

publications by international experts and may not coincide with the established practice in this field of knowledge.

CONCLUSION

The given schemes are aimed at a personalized approach to the clinical and laboratory diagnosis of the most common pregnancy complications and they bypass the standard solution of the problem. The bulk of the research methods included in the schemes are affordable and feasible and require standard laboratory equipment, which allows the proposed approach to be introduced into clinical practice.

Considering the versatility and ambiguity of opinions on the stated issue, we hope for in-depth analysis and comments from experts.

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