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Optimization of therapy for miscarriage in patients with acquired thrombophilia (Literature Review)

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Relevance: Thrombophilias are still one of the pressing problems in obstetric practice.The last decade of the 20th century was marked by the discovery of a large number of genetically determined and acquired thrombophilias, which repeatedly increase the risk of thrombosis and thromboembolism during pregnancy.Currently, there is no doubt that thrombosis is one of the main causes of fatal outcomes in the world. Many researchers indicate that for every 1000 births there are 2-5 cases of thrombotic complications [1, 2]. Up to 50% of venous thromboses occur in patients under 40 years of age and are usually associated with pregnancy. Some authors note that the risk of venous thromboembolic complications in pregnant women is 4-10 times higher than in non-pregnant women of the same age. The risk increases with the onset of pregnancy and becomes maximum in the postpartum period [16, 17].This may be due to the fact that all the classical components of Virchow's triad are present even in uncomplicated pregnancy and labor. Blood flow velocity in the vessels of the lower extremities decreases by almost 50%, changes in the hemostasis system occur (which are primarily manifested in the tendency

Purpose: The aim of this scientific review- To show the current scientific understanding of etiopathogenesis, clinic, diagnosis and risk factors of thrombophilia in pregnant women.

Method: Russian- and English-language scientific literature sources in recent years were analyzed. The increasing importance of risk factors, co-morbidities in the development of thrombophilia in miscarriage was established.

Result. We examined for thrombophilia those patients with a history of obstetric complications, habitual miscarriage, gestosis, placental insufficiency, antenatal fetal death, early neonatal fetal death in the first 7 days after delivery, as well as the presence of an aggravated anamnesis, TEE in the pedigree (especially during pregnancy) in those women who are just planning pregnancy. Patients with diabetes mellitus and liver diseases were not included in the study.

Conclusions. The results of the review and our own studies show the causative factors of thrombophilia, which cause a high risk of thrombohemorrhagic and obstetric complications. With timely initiation and adequate anticoagulant therapy, a favorable outcome is possible. Consequently, the high risk of thromboembolism in obstetric practice indicates the need for screening to detect hereditary thrombophilia [9].

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In conclusion of the section on conservative therapy, it should be emphasized that the prescription of anticoagulant drugs to pregnant women should be carried out according to clinical indications, which is especially relevant in groups of patients at high risk of thromboembolism. In some cases, such therapy is indicated to improve perinatal outcomes in the current pregnancy.

Obstetric complications due to abnormalities in the hemostasis system are associated with endothelial dysfunction and with arterial hypertension (AH).

In pregnant women with AH in all trimesters of pregnancy, thrombogenic shifts (hyperaggregation, hypercoagulability, slow fibrinolysis), as well as signs of endothelial dysfunction (decreased nitrite and nitrate levels, increased quantitative activity of von Willebrand factor) are detected significantly more often in the II trimester of pregnancy. The factors that have an independent influence on the cumulative unfavorable outcome are: presence of AH, preterm labor in the history and increased fibrinogen level in the II trimester of pregnancy [19].

A number of authors believe that in 35-42% of cases antiphospholipid syndrome (APS) is the cause not only of such obstetric complications as habitual pregnancy failure, antenatal fetal death, syndrome of delayed intrauterine development of the fetus, preeclampsia, but also recurrent thrombosis of various localizations [3, 4].

However, APS is by no means the only cause of hemostasis disorders that provoke obstetric complications. Many researchers note that due to the discovery of a number of genetically determined defects of hemostasis (mutations G1691A of factor V Leiden in the gene of factor V of the blood coagulation system and G20210A in the gene of prothrombin), it has become possible to explain previously incomprehensible cases of thrombotic complications [56].

N.V. Putilova in her publication dwells on the fact that the presence of hemostasis system gene mutations in a patient leads to the formation of hereditary thrombophilia and causes predisposition to the development of thrombosis [7].

This condition may not be complicated by thrombotic manifestations for a long time (sometimes throughout life). However, as a result of "provoking" factors, one of which is pregnancy, the risk of thrombosis in this category of patients increases significantly. To date, the adaptive changes in hemostasis during physiologic course of pregnancy, providing prevention of excessive blood loss in labor, which are most pronounced in the III trimester of pregnancy, are well studied. In this period of time there is an increase in the content of VII, X, VIII, V factors, fibrinogen, Willebrand factor.

A.M. Cumming et al. report that along with activation of the coagulative potential, inhibition of the anticoagulant system of blood is characteristic. This is manifested in increased resistance to activated protein C and decreased activity of protein S [8]. As a result, a slight activation of intravascular blood coagulation is observed in the ^{22} and ^{222} trimesters of pregnancy.

The results of scientific studies confirm the presence of genetic predisposition to thrombosis - hereditary thrombophilia, which explains the development of thrombosis, including thrombosis in the uteroplacental blood vessels. However, at the same time, as indicated by E.K. Aylamazyan and M.S. Zainulina, polymorphism of genes determining thrombophilia is found in healthy patients whose somatic and obstetric history is not aggravated [9]. This is confirmed by the data of P. Clarc et al. who conducted a study involving 4000 pregnant women and found no association between the presence of factor V Leiden gene mutation and unfavorable outcomes and complications of pregnancy, such as gestosis and delayed fetal intrauterine development [10].

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F.E. Preston et al. in a retrospective case-control study, which included patients from families with hereditary thrombophilia and thrombosis, found a significant increase in the risk of stillbirth in carriers of the most severe forms of thrombophilia (mutations in genes such as factor V Leiden, prothrombin [G20210A], MTHFR 677C/T, the presence of combined defects or deficiency of antithrombin III) [11]. E. Pey et al. in their meta-analysis also indicate the association of two or more episodes of pregnancy loss with the fact of carrying a mutation of the factor V Leiden gene [12].
Homozygosity for the MTHFR 677T polymorphism is not considered a risk factor.
At the same time, R.P. Murphy et al., who conducted a study involving 3020 patients, found no increase in the incidence of miscarriage of pregnancy in the III trimester, gestosis and fetal delay in carriers of the factor V Leiden gene mutation [13].
As pointed out by L.A. Creer et al., the ambiguity of the results suggests that to assess the degree of risk of pregnancy complications in thrombophilia, information on the genetic characteristics of the proband alone is insufficient. The risk, apparently, can be adequately assessed only by taking into account the phenotypic manifestations of genetic defects, which are manifested by clinical symptoms of thrombophilia and can be detected by coagulation studies [9, 14].
This is also confirmed by the results of the work of R. Rai et al., who in a study of 1000 patients found a more pronounced association of habitual pregnancy failure with acquired resistance to protein C than with the presence of a mutation of the factor V Leiden gene [15].
Russian scientists of the D.O. Ott Research Institute of Obstetrics and Gynecology have great experience in this matter. D.O. Ott Research Institute of Obstetrics and Gynecology, which has been dealing with the problems of thrombophilia for more than 12 years. Annually, 1500 studies of thrombophilic polymorphisms, more than 20,000 hemostasiologic studies are conducted. For the first time in Russia it was in this institute that the biochipping method was used to study thrombophilic polymorphisms. The results of studies show a high risk of thrombohemorrhagic and obstetric complications, which requires screening to determine hereditary thrombophilia [9].
Risk factors for thromboembolic complications (TEC) in obstetrics and gynecology are categorized into four levels by P.G. Lindqvist et al:
Level 1 (5-fold increased risk) - heterozygous mutation of the factor V Leiden gene; heterozygous mutation of the prothrombin gene; overweight; cesarean section; thrombosis in relatives under 60 years of age; female age over 40 years; preeclampsia/gestosis; placental abruption;
Level 2 (25-fold increased risk) - protein S and C deficiency; prolonged immobilization (bed rest); ovarian hyperstimulation syndrome; lupus anticoagulant; cardiolipin antibodies;
Level 3 (125-fold increased risk) is a homozygous prothrombin gene mutation;
Level 4:
high risk (10% absolute risk of VTE during pregnancy) - presence of a history of VTE; APS without a history of VTE;
very high risk (15% absolute risk of VTE) - mechanical prosthetic heart valves; long-term warfarin use; antithrombin III deficiency, recurrent thrombosis; APS and history of VTE [20].
Prolonged general anesthesia and immobilization can lead to thrombosis in the deep veins of the lower extremities [21]. According to L.A. Creer, the probability of TEE after cesarean section is about three times higher than after natural childbirth [14]. A.V. Murashko believes that it is surgical delivery by cesarean section that poses the greatest threat with regard to the occurrence of TEE [21].

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The degree of involvement of the venous system depends on the other factors of Virchow's triad: damage to the venous wall, alteration of normal blood flow, and hypercoagulability. Venous stasis may be a consequence of immobilization, whereas hypercoagulability may result from tissue damage, inflammation or malignancy, and pregnancy.

Selection of pregnant women for prophylaxis and treatment should be based on individual assessment of risk factors, type of thrombophilia, number of thrombophilic polymorphisms present, presence or absence of previous episodes of venous VTE in the anamnesis, as well as additional risk factors (age over 35 years, presence of concomitant cardiovascular and endocrine pathology).

Various mechanical and medication methods for the prevention of VTE are currently in use. Among them:

graduated compression stockings (so-called antithromboembolic stockings), which have a compression effect with a graduated distribution on the lower limbs, helping to reduce the distensibility of the venous wall and increasing the outflow of blood into the deep venous system. For example, venoteks, a modern compression product, is a high-tech product that exerts maximum compression in the distal limb, which is evenly reduced in the proximal direction;

devices for mechanical intermittent pneumatic compression, whereby the limbs are cyclically compressed and depressurized by the air injected into the compression product;

foot pump - a device that compresses the foot. It helps to increase venous return and, as a result, reduces stasis in the lower limbs;

anticoagulation therapy is given to pregnant women in the following cases:

deep vein thrombosis and pulmonary embolism during the present pregnancy;

mechanical heart valve;

APS (if correctly diagnosed);

in thrombophilia: antithrombin III defect, combination of hereditary thrombophilias such as protein S and C deficiency, resistance to activated protein C due to Leiden FV mutation, hyperprothrombinemia due to prothrombin G20210A mutation, hyperhomocysteinemia, mutation in plasminogen activator inhibitor type I gene;

a manifestation of arterial thrombosis;

An undeveloped pregnancy and decreased platelet and/or fibrinogen counts in preparation for uterine cavity emptying;

fetoplacental insufficiency confirmed by fetometry, Doppler study and/or hormonal studies, and/or cardiotocography [23].

The main goal of therapy is to prevent TEE, bleeding, improve blood circulation in the system mother-placenta-fetus, ensuring uncomplicated pregnancy and its prolongation.

According to a number of authors, a necessary and sufficient technique for the prevention of thromboembolic disease is the use of a risk assessment score and the prescription of anticoagulant therapy for prophylactic purposes, as is the case in general surgical practice [23, 24]. M. de Swiet points to the age of pregnant women as a prognostic sign and draws attention to the increased incidence of VTE in pregnant women over 40 years of age (100 times compared to the group aged 20-25 years) [26].

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Anticoagulant drugs most commonly used in obstetric practice
Unfractionated heparin (UFH)
Continuous intravenous infusion
According to J.S. Cinsberg et al., the success of treatment with UFH depends on a sufficient initial dose, which should be at least 30-35 thousand units/day. [25]. Such a therapy regimen is used in acute cases with mandatory monitoring of treatment efficacy and safety by activated partial thromboplastin time (APTT) [26].
Subcutaneous intermittent injection of UFH (Ginsberg J.S., 2003):
(a) Mini-doses: 5000 IU every 12 h without laboratory monitoring;
b) moderate doses: subcutaneously every 12 h with monitoring of changes in antifactor Xa content to 0.1-0.3 U/mL 6 h after injection;
c) adapted doses: subcutaneously every 12 h, with monitoring of changes in the ACEI to values 1.5-2 times higher than normal, 6 h after injection.
Inhalations

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Prof. V.I. Krasnopolsky et al. recommend heparin inhalation using an ultrasonic inhaler. Heparin is diluted with distilled water in a ratio of 1:4. Inhalations are performed 2 times a day with an interval of 12 h [23]. In order to prevent gestosis, the daily dose is 300 U/kg, the course duration is 7 days. Usually 2-3 courses with an interval of 2 days are required. For 10 days before delivery it is necessary to discontinue treatment.

For other indications, the daily dose is 500 U/kg, course duration - 21 days, number of courses - 1-2, interval between courses - 2 weeks. Treatment should be discontinued 14 days before delivery.

Low molecular weight heparins (LMWH)

NMG as well as UFH do not penetrate the placental barrier into milk, are safe for the fetus and are the drug of choice for the treatment of venous thromboembolism in pregnant women [25]. Fraxiparin is used as anticoagulant therapy in courses of 5-10 days or more in a single dose of 0.3 to 0.6 ml. Duration of use and dose of the drug is prescribed depending on body weight, clinical picture and the rate of normalization of hemostasis system parameters. In some cases, with persistent disorders of the coagulation system, treatment continues throughout most of pregnancy.

Monitoring the effectiveness of heparin therapy is carried out by the most sensitive laboratory test, which reflects the pharmacological effect of NMG, by determining the activity of antifactor Xa in plasma.

One of the effective NMG preparations is tinzaparin. According to K. Khasia et al., the dose of tinzaparin should be 4500 units/day at a patient's body weight less than 100 kg and 5000 units/day at a weight over 100 kg. The authors believe that the final dose of NMG should be established taking into account the activity of anti-factor Xa [27].

S. Schulman reports unsatisfactory perinatal outcomes for mother and fetus in patients with antithrombin III deficiency. Therefore, in order to prevent VTE it is advisable to prescribe NMG in a dosage capable of increasing the AHR in 1.3-1.5 times compared with reference values in 5-6 h after triple subcutaneous injections. It is also possible to use NMG with antifactor Xa activity indicator equal to 0.1-0.2 units/mL.

Antivitamin K (warfarin) has a possible teratogenic effect and increases the risk of bleeding in both mother and fetus. Therefore, it is recommended for use in pregnant women with artificial heart valves, in allergic reactions to heparin, and in the presence of a high titer of antiphospholipid antibodies [26]. A.F. Jacobsen et al., P.M. Sandset believe that antivitamin K does not penetrate into maternal milk and can be used in breastfeeding women [29].

Treatment with aspirin is usually carried out in combination therapy with heparin. M. Rohathi confirms the effectiveness of 75 mg aspirin in combination with subcutaneous injection of 5,000 units of heparin at 12 h intervals or in combination with the use of NMG parnaparin at a dose of 0.3 ml subcutaneously in patients with the presence of antiphospholipid antibodies and habitual miscarriage to improve perinatal parameters[30].

When diagnosing deviations from the norm in the indicators of the blood coagulation system, it is necessary to carry out prophylaxis with the use of antiaggregants (curantil and thrombo-ACS), anticoagulants (preferably using NMG), as well as multivitamins containing B vitamins and folic acid.

If surgical prophylaxis of pulmonary embolism is necessary during pregnancy and in the postpartum period, cavaclipping may be used as a reliable and safe method [18].

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