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Antithrombotic therapy of pregnant women suffering from certain congenital cardiopathologies

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Abstract

The paper discusses the features of antithrombotic therapy of pregnant women suffering from congenital cardiopathologies. Providing medical care to women suffering from cardiovascular diseases and carrying a child is a difficult task due to the unique maternal physiology, which causes profound changes in many organ systems. First of all, such difficulties are caused by the presence of the fetus, since individual approaches to the treatment of cardiac diseases of the mother can have an adverse disease on the child. Conversely, the patient's refusal of the necessary treatment due to potential harm to the fetus is fraught with a bad outcome for both the mother and the child. Physiological adaptation of the mother's body during pregnancy can provoke cardiometabolic complications and cause thrombosis, the consequences of which can be fatal. Accordingly, the development of approaches to the organization of antithrombotic therapy of pregnant patients with cardiopathologies can contribute to improving the survival of the mother and fetus during pregnancy, as well as create prerequisites for a successful delivery and postpartum recovery of the woman and child.

Keywords

Pregnant women, Congenital cardiopathology, Cardiometabolic complications, Antithrombotic therapy

Imprint

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Introduction

Cardiac pathologies are widespread in the world and today are the main cause of death of people. Cardiopathologies can be both congenital and acquired under the influence of a number of negative factors.

Congenital cardiopathologies are a serious predictor of risk for women during pregnancy. Every year more and more patients with this disease reach reproductive age, and cardiovascular diseases of pregnant women have become the most common cardiac pathology during fetal gestation [1].

Blood circulation and hematological adaptation during pregnancy, which occur with increased metabolic needs, along with bleeding, pain and anxiety during childbirth and delivery, pose serious problems for the heart, lead to various complications and mortality in women with congenital cardiopathologies [2].

A particular danger for women who are preparing to become a mother is the congenital heart defects (CHD) diagnosed in them; complications of such, even in the absence of stress on the body caused by pregnancy, can be arrhythmias of various nature, stroke, endocarditis, heart failure and pulmonary hypertension [3]. Moreover, against the background of heart defects, women may develop classic acquired cardiovascular diseases, such as coronary heart disease.

A significant part of patients diagnosed with CHD at various stages of life need cardiac surgical correction, as well as implantation of biological or mechanical heart valves, while prosthetic valve thrombosis is a dangerous complication with an annual frequency of 0.1–6%, depending on the type of prosthesis and its position [4].

Thromboembolic complications (TEO) are another complication that has a significant impact on mortality and morbidity in patients with congenital cardiopathologies [5]. However, clear recommendations for anticoagulant therapy in these patients are difficult to establish due to the heterogeneity of their population. Accordingly, in order to reduce the risk of the above complications, it is necessary to carry out the necessary therapeutic measures to prevent thrombosis

in women with congenital cardiopathologies during pregnancy.

Materials and methods

In the process of writing the paper, theoretical and practical material devoted to the study of the main aspects of the research topic was studied, as well as the conclusions of clinicians offering various options for therapeutic approaches to reduce the risk of blood clots in pregnant women with a history of cardiopathology were studied. The main methods used in the process of working with the material were the comparison method, the analytical method, as well as the induction method.

Results

The development of thrombosis in particular and thrombotic disease in general in a woman during pregnancy becomes possible due to a number of factors, the combination of which forms a favorable environment for the formation of venous and arterial blood clots. Low physical activity of a woman, as well as dehydration of the body due to vomiting of pregnant women, predetermine the conditions for the development of thromboembolic complications. Researchers note that the risk of thrombosis increases several times during pregnancy, and changes that support hypercoagulation occur already in the first trimester [6].

Pregnancy, proceeding without pathologies, is accompanied by changes in the coagulation and fibrinolytic systems. At the same time, there is an increase in the level of fibrinogen, soluble fibrin, D-dimer, plasminogen activator inhibitors 1 and 2, and there is a positive result for antibodies to cardiolipin. In addition, the level of individual blood clotting factors (I, VII, VIII and XII) increases, while the levels of free protein S decrease [7]. Activated protein C is also reduced. In the vast majority of pregnant women, these levels do not change enough to cause a problem, besides, these changes help prevent prenatal blood loss. However, they can have devastating consequences for women with a history or previously undiagnosed thrombophilia.

Fibrinogen, also known as coagulation factor I, is involved in the construction of a fibrin network in clots and platelet aggregation. The concentration of factor I (fibrinogen) increases in pregnant women, starting from about the 20th week of pregnancy, and reaches the level of 400 mg/100 ml. [8]

Protein S deficiency is a known cause of venous thrombosis. Protein S is a cofactor of protein C. The free form of protein S is active in disrupting the blood clotting cascade. During pregnancy, there is a significant decrease in the activity of protein C and protein S during normal pregnancy compared to the postpartum period. When factor Va is resistant to protein C (APC-resistance) The anticoagulant effect of protein C is reduced, which leads to blood clotting disorders and may be the cause of thrombophilia [9].

The above mechanism is extremely dangerous for pregnant women with congenital cardiopathologies, including those who at one stage or another of life required surgical correction and implantation of mechanical or biological valves. In this regard, increased attention of specialists should be organized to such patients from the first day of their pregnancy detection.

Prenatal interdisciplinary assessment is necessary to assess the cardiovascular and obstetric risk of the patient, depending on one or another congenital cardiopathology. Obstetric assessment includes determining the risk of miscarriage, premature birth, preeclampsia, genetic transmission and fetal complications. A care plan should be developed that defines obstetric and cardiological control during pregnancy, as well as the method of delivery.

Fetal and newborn outcomes are closely related to the severity of congenital cardiopathology, and predictors of adverse outcomes include NYHA≥II class, maternal cyanosis, left heart obstruction, and the use of anticoagulants. In particular, one of the possible risks may be a decrease in the growth rate of the fetus. Experts believe that the use of aspirin at the beginning of < 16 weeks significantly reduces the frequency of fetal growth retardation and preeclampsia [10].

When choosing anticoagulant therapy, the risks and benefits for the mother and fetus should be weighed. Since vitamin K antagonists (VKA) freely penetrate the placenta, these regimens are associated with a significant risk of adverse events for the fetus.

Fetotoxicity includes embryopathy of warfarin in 0.6–10% and fetopathy in 0.7–2% of pregnancies when it is used in the first and second/third trimester, respectively. As a result, fetal warfarin syndrome (FWS) is manifested, which includes hypoplasia of the nasal cartilage, limb defects, hypoplasia with or without dotted epiphyses, as well as mental retardation. There is also a decrease in fetal weight up to 40% to normal and there is a risk of neurological complications [11]

The risk of warfarin embryopathy depends on the dose and time, i.e. it is especially high when exposed during the first trimester and when the daily dose exceeds 5 mg. It should be noted that the effect of vitamin K antagonists (VKA) on the fetus after the first trimester increases the risk of defects of the central nervous system, ocular abnormalities, probably caused by micro-hemorrhages in the tissues of neurons, and cerebral ventricular hemorrhages [12].

Unfractionated heparin (UH) and low molecular weight heparin (LMWH) are safe for the fetus because they are large molecules that do not penetrate the placenta, unlike VKA . Direct oral anticoagulants (DOA) are currently contraindicated in pregnant women, since the available data are insufficient to exclude the risk of embryotoxicity.

Experts note that the frequency of preterm labor increases significantly to 16% in women in labor with congenital cardiopathology, antenatal corticosteroid therapy (ACT) should be considered in relation to individual patients between the 24th and 33rd weeks [13]. It reduces the frequency of respiratory distress syndrome, thereby improving the survival rate of premature babies.

Induction of labor should be considered at the 40th week of pregnancy in all women with heart disease. Vaginal delivery is the first choice for most patients, and cesarean section should be performed only for obstetric indications. Cesarean section should be preferred for patients admitted to labor for VKA in order to reduce the risk of intracranial hemorrhage of the fetus. It is also recommended to cancel anticoagulant therapy in case of urgent childbirth.

Discussion

For certain clinical situations within the framework of the topic under consideration, a number of recommendations are presented in the literature.

Cardiac arrhythmia (CA) is a frequent complication in congenital cardiopathologies in pregnant women, increasing both mortality and morbidity. Even simple secondary defects of the atrial septum (DAS) are associated with an increased risk of LDC, which increases, in particular, with the transposition of the main arteries after atrial switching surgery [14].

Long-term anticoagulant therapy is recommended for patients with congenital cardiac pathologies when the risk of relapse is high. Women of childbearing age with moderate or complex pathology and CA on the background of anticoagulant therapy are not uncommon, and the treatment regimen with anticoagulants is an important point to discuss before pregnancy.

CA may develop during pregnancy due to the already mentioned hemodynamic changes. There are few recommendations, but catheter ablation can be considered if minimal ionizing radiation is used. Direct current cardioversion may be preferable to medical cardioversion in unstable patients, since it is highly effective and safe [15].

Pregnancy in women with Fontaine circulation is considered a high- and very high-risk pregnancy, especially in the case of pre-existing CA or reduced ventricular function. The risk of cardiac and obstetric complications in the mother, as well as complications in the fetus and newborn is increased: up to 8.4% - for the detection of CA, up to 69% – for miscarriage, up to 50% – for postpartum bleeding and premature birth. The benefit-risk ratio should be assessed on an individual basis when discussing anticoagulants in pregnant women with Fontaine circulation.

Pulmonary embolism and deep vein thrombosis occur in approximately 0.03–0.20% of all pregnancies and are the cause of 3.5% of deaths in all cases [16]. With these pathologies, specialists recommend LMWH, the advantage of which, compared with UH, is a lower frequency of osteoporotic complications. Monitoring of the anticoagulant effect of LMWH should be carried out on an ongoing basis.

Pregnancy in patients with a mechanical heart valve is a high-risk situation, which reflects their assignment to group III according to the WHO risk classification [17]. Here, maternal mortality and morbidity are 30-200 times higher, not only in comparison with pregnant women without valve prostheses, but also with patients with biological valve prostheses. The outcomes for the mother and fetus deteriorate significantly: only 28-58% of patients have a pregnancy without complications, and the children are born alive. The presence of a mechanical heart valve is a predictor of events for the mother and fetus. The increased risk may mainly be associated with thrombosis and hemorrhagic complications due to difficulties in achieving effective anticoagulant therapy and its control.

The frequency of thromboembolic complications in such patients is high and occurs in 16% of cases. The researchers note that most valvular thrombosis occurred during the first trimester due to the replacement of VKA with LMWH or UH. This indicates the

subtherapeutic levels of heparin in the phase of transition from VKA to heparin as the main cause, and not pregnancy-induced hypercoagulation, which is most pronounced at the end of pregnancy [18]. Therefore, careful monitoring of the effectiveness of anticoagulants in hospital settings is crucial.

An important aspect in this context is the counseling of a woman before pregnancy, which should actually begin with the choice of a prosthesis. Since the effect of VKA on the fetus depends on the dose, some experts advocate determining the expected required dose of VKA , which can serve as a guideline for the patient and the doctor when choosing a valve prosthesis. However, the patient and the father of the unborn child should be informed that there is no risk-free strategy for anticoagulant therapy. It is necessary to develop a treatment plan with an assessment before pregnancy and a strategy for each trimester, delivery and postpartum period, which, of course, must be adapted according to the development during pregnancy.

In recent years, two different anticoagulant therapy strategies have been developed for pregnant patients with congenital cardiopathologies: the VKA -based approach and the LMWH-based approach.

For historical reasons, most of the data is based on VKA -based schemas. As mentioned above, VKA S effectively protect against maternal complications with a risk of thrombosis and maternal mortality < 3% and < 1%, respectively; however, these low risks should be balanced by a significant risk of warfarin embryopathy and neurological complications [19].

To avoid warfarin embryopathy, it is proposed to replace VKA with either UH or LMWH during the first trimester, which increases the risk of thromboembolic complications by up to 9%. LMWH is usually chosen, which is confirmed by a recent study [20].

The use of VKA throughout pregnancy is an alternative for patients who require only a low dose of VKA (warfarin < 5 mg, phenprocumon < 3 mg, acenocumarol < 2 mg) [21]. Several studies have demonstrated a low incidence of thromboembolic complications when using this regimen. However, this strategy is still associated with a 20% risk of fetal loss, which does not depend on the dose of VKA.

The use of LMWH throughout pregnancy is an alternative to the VKA scheme. LMWH does not penetrate the placenta, which eliminates the risk of any embryopathy and reduces the risk of bleeding. Usually, the dose of LMWH is selected depending on the patient's body weight. However, the renal clearance of LMWH increases, as well as the volume distribution, which requires careful monitoring and dose adjustment. The initial dose adjusted for body weight often has to be rapidly increased by 54% during the first trimester [22].

As mentioned earlier, direct oral anticoagulants (PPAC) are currently contraindicated during pregnancy. The first randomized study comparing dabigatran with warfarin in non-pregnant patients with congenital cardiopathologies revealed a significant risk of thromboembolic complications. However, a recent pilot study evaluating rivaroxaban in low-risk patients found no cases of the above complications. As mentioned earlier, the safety and efficacy of PPAC must be proven in non-pregnant and consistently in pregnant patients before their routine use can be recommended.

In the absence of randomized studies comparing various strategies for reducing the risk of thrombosis in pregnant women with cardiopathology, several retrospective studies and meta-analyses have been published in recent years to help choose the best approach for each patient. Thus, researchers compared VKA and heparin regimens during the first trimester in a meta-analysis [23]. Their results showed that VKA regimens better protect against thrombosis and further complications than regimens with heparin. There were no differences in relation to adverse outcomes for the fetus, which occurred, however, relatively often, in about 17-19%, with all regimens.

The researchers also determined that the combined risk to the mother was lowest with the VKA scheme, while the risk to the fetus was lowest with the LMWH scheme. Fetal complications occurred in 40% of cases when using VKA [24].

NSF regimens were associated with the highest mortality rate of 3.4%. Anticoagulant embryo- or fetopathy occurred in about 2% in the VKA group, 1.4% in the NG/LMWH +VKA group, but was not observed in the LMWH group. The latter regime was also associated with the highest live birth rate – 92% [25].

It can be concluded that schemes with VKA protect the mother, and schemes with LMWH protect the fetus. The observed higher risk of thromboembolic complications in patients receiving LMWH should be considered with caution.

An important issue is the use of optimal strategies for the treatment of LMWH in pregnant women

with mechanical heart valves. The main purpose of anticoagulant therapy of such pregnant women is to prevent valve thrombosis and its fatal consequences for both mother and fetus. Although VKA S are considered the most effective regimen for the prevention of thromboembolic complications associated with pregnancy, they are associated with a significant risk of fetal complications, including embryopathy and miscarriage. Therefore, in most pregnant women, VKA S (temporarily or throughout pregnancy) are replaced by LMWH, which do not penetrate the placenta and, therefore, do not have a direct effect on the fetus [26].

Due to predictable pharmacokinetics and pharmacodynamics, routine monitoring of the effectiveness of LMWH is generally not considered necessary. However, during pregnancy, a fixed dose of LMWH seems to be associated with an unacceptably high level of complications in the mother. Therefore, under these conditions, the activity of anti-Xa is measured to determine the dosage of LMWH therapy. Nevertheless, in pregnant women with a mechanical heart valve, both the target level of anti-Xa and the optimal monitoring schedule are still a matter of debate.

A number of studies have demonstrated that monitoring peak levels of anti-Xa, as recommended in current guidelines, is not a reliable indicator of the effectiveness of anticoagulants [27]. Despite adequate targeted peak levels of anti-Xa, pregnant women with a mechanical heart valve may still develop valve thrombosis, and recent studies show the importance of adding routine measurements and maintaining minimum levels of anti-Xa to ensure adequate anticoagulant therapy.

During pregnancy, the dose of LMWH needed to maintain the therapeutic level of anticoagulants may increase. Experts indicate that during pregnancy, 85% of women with a mechanical heart valve need an increase in the dose [28]. Therefore, strict monitoring and good adherence to the treatment regimen are considered mandatory while taking anticoagulants.

A limitation of the use of LMWH for anticoagulant therapy during pregnancy is their renal clearance. Due to significant pregnancy-related changes in maternal physiology with an increase in renal clearance and a higher volume of distribution, the anticoagulant effect of LMWH 2 times a day in some patients may not be sufficient to maintain adequate minimum and peak levels of anti-Xa. Accordingly, since the apparent half-life of LMWH is shorter in pregnant women, it can be assumed that in some patients, LMWH 3 times a day may be required to achieve a continuous adequate level of anticoagulation.

Conclusions

Thus, it can be concluded that the need for anticoagulant therapy during pregnancy significantly increases the risk of hemorrhagic and thromboembolic complications in the mother, mortality and adverse events in the fetus, such as miscarriage or intracerebral hemorrhage. Patients with congenital cardiopathologies present a particularly high risk: less than 60% tolerate pregnancy without any complications from the fetus or mother.

Counseling before pregnancy is a necessary event, and patients, together with their partners, should participate in decision-making on the choice of an individual anticoagulant strategy. Also, patients with congenital cardiopathologies during pregnancy should be in specialized centers under the supervision of multidisciplinary teams of hematologists, obstetricians, cardiologists and anesthesiologists with experience in high-risk pregnancy.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The authors read the ICMJE criteria for authorship and approved the final manuscript.

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