COMPARATIVE DYNAMICS OF THE EFFICIENCY OF ANTITHROMBOTIC PROPHYLAXIS BEFORE DELIVERY IN PREGNANT WOMEN WITH DIFFERENT FORMS OF ANTIPHOSPHOLIPID SYNDROME

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Abstract

Objectives: The aim of this study was the assessment of effectiveness of antithrombotic prophylaxis in pregnant women with different form of APS.

Methods of study: For the assessment of condition and effectiveness of treatment of pregnant women, the investigations were carried out in 92 women. In various periods of pregnancy were determined non-active thrombin-antithrombin III (TAT) complex, prothrombin fragments (F1+2), D-dimer etc.

Results and conclusions: Long-term antithrombotic prophylaxis with low-molecular heparins allows to decrease the level of thrombophilic markers in pregnant women with different forms of APS. Monotherapy with low-molecular heparins in women allows to normalize the level of thrombophilic markers and effectively prevents thrombosis.

Keywords

pregnancy, antiphospholipid syndrome, thrombosis, antithrombotic treatment

Introduction

According to a some number of authors, the main cause of thrombotic complications is the antiphospholipid syndrome (APS) characterized by hypersecretion of antibodies to phospholipids found in pregnant women. The circulatory period of antiphospholipid antibodies (APA) during this disease and the multifactor injury of the haemostasis system make this autoimmune process extremely dangerous for thrombotic complications. In most cases, additional risk factors such as pregnancy and postpartum period are needed to achieve thrombophilia condition in women. Abdominal delivery is also considered a serious risk factor in this regard. Obstetric practice shows that thrombosis and thromboembolism occur more frequently in the postpartum (postoperative) period. The main cause of thromboembolic complications is the postpartum long-term bed regimen and the use of estrogens for weakening of lactation. In addition, some studies have shown that 75% of deep vein thromboses occur during the antenatal period, with 1/3 to 1/2 of the thrombotic cases present before the 15th week of pregnancy. Other researchers report that deep vein thromboses is found at the same frequency in all three trimesters of pregnancy.

Pregnancy increases the risk of thromboembolism by 5-6 times in women, while abdominal birth increases the risk of thrombosis by 10 to 15 times. Death rate from thrombotic complications after cesarean section is increased by 10:1 compared with vaginal delivery. On average, 7 to 15% of women with thrombosis in the previous pregnancy (from 0.5 to 21% according to various authors) will have thrombotic complications in the next pregnancy. Increasing physiological hypercoagulation during pregnancy puts issues that are unique to researchers.

Given the above, APA's antenatal diagnosis, as well as early diagnosis of APS are extremely urgent, and the prevention of thrombotic complications is based on this category of pregnant women. The main purpose of the study was to compare the efficiency of antithrombotic prophylaxis in pre-cesarean section period in pregnant women with different forms of APS.

Material and Methods

The basis of the study was the analysis of the results of clinical observations and laboratory examinations carried out on pregnant women with various forms of APS in the Scientific Research Institute of Obstetrics and Gynecology and in the Department of Obstetrics and Gynecology of the AMU (Azerbaijan Medical University) in 2008-2014 years.

Based on the above-mentioned clinical-laboratory criteria, 92 patients were included with age from 19 to 41 years old, which consisted of 3 basic examination groups. The

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first and second groups included 64 patients who were fully compatible with clinical and laboratory criteria of antiphospholipid syndrome.

The first group included 35 primary APS, the second group consisted of 29 pregnant women with secondary APS (autoimmune diseases of connective tissue - lupus erythematosus, rheumatoid arthritis, etc.) and third group included 28 pregnant women with serological symptoms of APS.

It was determined the scope of the measures taken by the research. These measures include the scrutiny of the anamnestic data, providing testing on the lupus anticoagulants and the anticardiolipin antibodies, and correction of the haemostasis and circulatory disorders of pregnant in antenatal period with the aim to develop of adequate preventive measures.

The control group consisted of 22 patients with no lupus anticoagulant and no antiphospholipid antibodies (negative-test) and physiologically normal pregnancy, which led to the creation of a comparative group. There are no hereditary and allergic diseases in these pregnant women. The average age was 29.4±4.1 years. The tests began with the first trimester of pregnancy, and followed by 21-23 weeks, 27-28 weeks and 32-34 weeks. The determination of the presence of inactivated thrombin-antithrombin III (TAT) complexes was carried out by immunofluorometric method in the "Boehringer-ELISA-Photometr" spectrophotometer with the help of the kit "Enzygnost-TAT" (Boehringerwerke, Germany). The concentration of the F1+2 fragments of the protrombin was determined by the immunoferment method in the blood plasma sample which was studied with the help of the kit "Enzygnost F1+2" (Boehringerwerke, Germany). For this purpose microbial cells of coagulase-negative staphylococcal strains with adhesion capability were used in the presence of fibrin monomers, as well as fibrin degradation products (FDP). Determination of D-dimer was based on the interaction of the high-specific antibodies with the D-dimer fixed on latex particles by the help of latex testing "Dimertest" (Agen, Austria). The study of the platelets aggregation was performed by the Born method in the aggregometric "Chonolog" (France). The principle of the method is based on the photoelectric recording of the dynamics of the optical density of the plasma sample riched by platelets during mixing with aggregate inducers. 1x10^{-3} M, 1x10^{-5} M, 1x10^{-7} M Adenosindiphosphate (ADP) solution, 1x10^{-6} M Adrenaline solution, 1x10^{-5} M Ristocetin solution and 0.04 mg/ml collagen solution were used as aggregate inducers.

The statistical analysis was carried out taking into account modern recommendations of all calculation and figures taken during the research work. The non-parametric method - Wilcoxon (Mann-Whitney) was used to determine the difference between indicators taking into account the number of indicators in the groups.

**Results**

The determination of the number of platelets in the peripheral blood during treatment with using small-molecular heparin was administered before beginnig the treatment, on 7-10 days after and every next 6 days after the treatment beginning. It was noted the positive dynamics associated with normalization in the number of platelets after the assignment of fraxiparine. Thus, on the 10th day of treatment, in the 2nd trimester and in the third trimester, no significant dynamics were found in patients with primary disorder, nor in the whole group. It was not detected the thrombocytopenia induced by heparin in all groups during the observation period. On the contrary, we have seen that the number of platelets during the treatment by fraxiparine has increased in comparison with the period before treatment. This sign has been more apparent in pregnant women of the III group with circulating antiphospholipid antibodies (Figure 1).

![Figure 1. Comparative characteristics of average platelet number of different groups patients in different periods](image1)

**Dynamic control of aggregation parameters of platelets**

proves that fraxiparine has a significant detrimental effect on the aggregation of platelets induced by ADP- and Ristocetin. The highest inhibition effect was recorded on the 7-10th day of treatment (Figure 2).

![Figure 2. Aggregation of platelets in Ristocetin stimulation (%)](image2)

The effect of fraxiparine on aggregation activity of platelets was assessed on 10 days after treatment, in 20-28 weeks of pregnancy and one day before delivery in all three groups. On the 10th day of small-molecular heparin administration it was not observed hyperfunction of platelets during the use of the adrenaline, ADP and Ristocetin as an inducer of stymulation. Early hyperactivation of the platelets was eliminated after the administration of the fraxiparine and it was normalized the aggregation of platelets.

It was determined the increasing of thrombin-antithrombin complex concentration in pregnant women with antiphospholipid syndrome, included in the main groups, during the period prior to the use of small-molecular heparin (fraxiparine). Thus, in the first group before the treatment, this
indicator was $6.8 \pm 2.1$ mcg/l, in the II group - $6.5 \pm 1.1$ mcg/l and in the III group it was $6.2 \pm 2.6$ mcg/l ($p < 0.01$) (Figure 3).

Discussion

Based on the results of the clinical and laboratory findings of pregnant women with primary and secondary APS, as well as APA circulating in blood of pregnant women, it is possible to judge the efficacy of small-molecular heparin in patients of this category. Antithrombotic therapy with using of the prophylactic dose of small-molecular heparin allowed preventing thrombophilia in Group III, as well as laboratory symptoms of developing chronic disseminated intravascular coagulation (DIC) syndrome in 7 to 10 days of treatment in I and II groups. It was used the small-molecular heparin - fraxiparine (225 ICU/kg, twice daily) was used to eliminate apparently significant changes in one case in each of the second and the third groups.

The results of study allow to say that blood coagulation activity is decreased sufficiently in pregnant women with an antiphospholipid syndrome and a high risk of thrombotic complications. As can be seen on the Figure 2, it has been possible to maintain the normalization of platelet aggregation up to the time of delivery, which is important for the prevention of thrombotic complications. The 28-30 weeks of pregnancy is optimal time to control of the platelets circle function in haemostasis, also to provide timely correction in cases of clinical complications in the gestational process during the treatment by the small-molecular heparin.

In our observations, we have never encountered with heparin induced thrombocytopenia by the using fraxiparine. Progressive reduction in the number of platelets detected during before treatment period in 6 pregnant (I and II groups) was considered as thrombocytopenia of depression.

In our study was performed the determination of intravenous coagulation markers to assess the efficacy of therapy. When evaluating the practical positive effect of small-molecular heparin in the prevention of thrombophilia complications, we concluded that even if the prophylaxis is performed in early pregnancy and in the constant regime, and DIC syndrome symptoms were not developed it is not the direction to stop the antithrombotic therapy. Positive dynamics were observed following the normalization of platelets after defining small-molecular heparin and removing DIC syndrome. In one case, initial thrombocytopenia required corticosteroid therapy. No evidence of the prolonged ART and APTT indications was found in the control examinations. Taking into account the possibility of the influence of the amplification effect, we did not use small-molecular heparin and antiaggregant therapy at the same time.

Thus, according to our observations on the treatment of small-molecular heparin in long-term uninterrupted schedule in pregnant women with primary and secondary APS, we have concluded that in pregnant women of this category, antithrombotic prophylaxis should be performed using small-molecular heparin from a molecular heparin in the prevention of thrombophilia complications, included in the main groups during the period before the use of small-molecular heparin (fraxiparin) (Figure 4).
No need for permanent haemostasis screening during long-term use, minimal number of side effects, and positive acceptance by patients allows small-molecular heparin to be used as an antithrombotic prophylaxis and treatment choice in pregnant women with antiphospholipid syndrome.

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