Pregnancy, puerperium and neonatal outcome in patients with known deficiencies of protein S, and AT – case study

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Abstract

Pregnancy is a condition conducive to the development of thrombosis. The risk of thrombosis in pregnancy is about 3-5 times higher than in non-pregnant women. Congenital deficiency of protein S as well as antithrombin deficiency are inherited thrombophilias which significantly increase risk of thrombosis. We demonstrated two clinical situations the course of pregnancy, puerperium and neonatal outcome of two patients: with protein S and antithrombin deficiency.

Key words: antithrombin deficiency, congenital deficiency of protein S, thrombosis, pregnancy, puerperium

Introduction

Pregnancy is a condition conducive to the development of thrombosis, which is a form of thromboembolism – VTE [1]. The formation of a blood clot in a vein follows the Virchow’s triad: stasis of blood flow, the prevalence of prothrombotic factors over fibrinolytic factors and damage to the vessel wall [2]. Also the hormonal changes in pregnancy, especially high concentrations of progesterone, cause relaxation of blood vessels [3]. In addition, the mechanical pressure of the uterus on the iliac veins and vena cava slow blood flow and lead to the stasis in the veins of the lower extremities. Also relevant is the increase in the concentration of coagulation factors VII, VIII, X, and fibrinogen. The risk of thrombosis in pregnancy is about 3-5 times higher than in non-pregnant women [4]. The risk factors most strongly associated with the occurrence of thrombosis include mainly history of thrombosis and caesarean section.

The occurrence of congenital thrombophilia such as factor V Leiden mutation, protein S deficiency, protein C, antithrombin, prothrombin gene polymorphism or acquired forms like antiphospholipid syndrome, significantly increases the risk of thrombosis by increasing prothrombotic factors in the hemostatic balance [5]. They occur in approximately 8-15% white population, but are responsible for approximately half of the observed cases of thrombosis during pregnancy and puerperium [6].

Protein S is a vitamin K-dependent protein C cofactor, isolated in Seattle for the first time, hence the name. It comes in two forms – complement bound – C4b-binding protein and free form [7]. Only the free form has a protein C cofactor activity. In the presence of activated protein C it inactivates factor Va and VIIIa, leading to decreased formation of thrombin [8]. Protein S also enhances fibrinolysis activated by protein C, as well as indirectly (by other factors) inhibits the activation of prothrombin [9]. Congenital protein S deficiency was first detected in 1984. It is inherited in an autosomal dominant fashion, and these heterozygous families often experience recurrent thrombosis [10]. There are three known types of protein S deficiency: type I – classical, so-called quantitative deficiency, which is observed in the presence of about 50% of the normal protein S, with a marked free protein reduction and its weak activity, type II, with qualitative defect, in which we have to deal with normal protein S and its free form, but they lack normal activity; in type III we observe the normal values of protein S, with reduced values of the free form and reduced activity [11, 12]. According to some authors, this type resembles type I protein S deficiency, and can be caused by aging. The clinical picture of protein S deficiency is associated with spontaneously occurring (58%) of induced cases of thrombosis, with the average age of the first incident about 30 years of age [13]. It should also be noted that situations such as pregnancy or taking oral contraceptives, may lead to a acquired reduction in the level of protein S, together with the occurrence of thrombosis in patients previously asymptomatic [14]. During pregnancy, a decrease in the amount of protein S by about 70%, which may overlap with previously occurring congenital deficiency of pro-

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tein S, leads to conditions such as preeclampsia, IUGR, or thrombosis in the mother.

Antithrombin is the natural anticoagulant independent of vitamin K. It inhibits thrombin and other procoagulant factors, such as serine proteases Xa and IXa [15]. After administration of heparin, there is an observed growth of its activity, hence the name of heparin cofactor. Antithrombin exists in two forms, a monomer – which is biologically active, and in inactive form. Inactive form bound to the active form, gives rise to a heterodimer that is also not biologically active [16]. Antithrombin deficiency, detected for the first time in 1965, was the first specific factor of acquired thrombophilia. There are two subtypes of antithrombin deficiency. Type I – in which there is an observed reduction in the synthesis of antithrombin (AT) and type II in which there is a defect in the structure of AT leading to weakening of its functions in normal standard immunoassays [17]. Signs of AT deficiency are dominated by severe forms of venous thrombosis. The thrombosis events usually occur during pregnancy, oral contraceptives use or after injury. In 42% of cases there can be spontaneous thrombosis [18]. The incidence of acquired immunodeficiency AT is determined to 0.5 to 1% [19].

Clinical Situation # 1

A 30 year old patient admitted to the Division of Reproduction in June 2008 at 12 weeks of gestation. In 2007 she underwent laparoscopy during which endometrial ovarian cyst was removed. In the next month, the patient developed pneumonia. During the treatment of pneumonia, there was a deep vein thrombosis of the lower limb on the right. In early pregnancy she had experienced venous embolism in the upper limb where the venflon was placed. Hematologist implemented the enoxaparin 60 mg once daily and compression stockings.

Additionally dietary supplementation with calcium and symptoms of preterm labor. By the end of the pregnancy was complicated by oligohydramnios (AFI 5.8 cm) and symptoms of preterm labor. By the end of the pregnancy only small amount of amniotic fluid remained. At 38 weeks patient spontaneously gave birth to a boy weighing 2970 g, in good general condition (Apgar 10).

In four weeks postpartum with enoxaparin 60 mg once daily the patient experienced right lower extremity thrombosis. Enoxaparin dose was increased to 60 mg every 12 hours, and after puerperal period, warfarin was introduced at a dose of 2 mg.

In April 2009, she has been consulted again by hematologist, because of past history of thrombosis – they recommended maintenance dose of acenocoumarol 2 mg/day. In July 2009, there was another episode of thrombosis of the left lower limb. In the course of further investigations diagnosis of protein S deficiency reached 16% of the normal 55% activity. It was recommended to the patient to continue the use of acenocoumarol 2 mg/day. Haematological tests were conducted in a child of the patients, which also found decreased levels of protein S.

In March 2010, the patient was in the 7th week of second pregnancy. Due to the four episodes of thrombosis the patient received enoxaparin 60 mg every 12 hours. Control platelet count was > 200 thousand. The activity of anti-Xa factor was normal. Pregnancy developed without problems. In the 27 week low molecular weight heparin dose was increased to a therapeutic dose of 80 mg every 12 hours, which continued until the end of pregnancy. In the 34th week of pregnancy the patient experienced symptoms of preterm labor. Amount of amniotic fluid was normal – AFI 9.8 cm. At 38 weeks pregnant patient spontaneously delivered a boy 2980 g, Apgar 10. The histopathology of the placenta revealed massive reduction of exchange surface area and disturbances in maternal and fetal circulation. Tenth part of the placenta was covered by infarctions.

During puerperium the patient used enoxaparin 80 mg once daily. After 6 weeks of treatment with low molecular weight heparin anticoagulation was switched to acenocoumarol at a dose of 6 mg. Based on the results of coagulation tests (INR) it was adjusted to 8 mg, and in the further months it was increased to 18-20 mg. Hematologist recommended that the patient use of acenocoumarol for life.

Clinical Situation # 2

Patient at 18 years of age experienced deep vein thrombosis of the lower left limb. The episode occurred during second year of the use of combined oral contraception. The patient was diagnosed with antithrombin deficiency – at a level of 39.4%. Subsequent evaluations showed an increase to 70% AT with standard 84-120%. A family history of thrombosis was uneventful.

Patient was admitted to the Division of Reproduction in the first 8 weeks of pregnancy while already on recommended by the hematologist enoxaparin 60 mg once daily. The course of the early pregnancy was complica-
thrombin deficiency was established at 14%. The presence of thrombus was confirmed by ultrasound. Anti-Xa factor activity was used to monitor the treatment, and the symptoms almost completely disappeared. The child was discharged from the hospital in 37 day of life with a recommendation to continue the use of low molecular weight heparin and control in the Outpatient Hematology and Vascular Clinic. Other recommendations did not differ from the standard – breast feeding and taking vitamins.

**Discussion**

Thrombophilia means predisposition to thrombosis. The most common hereditary thrombophilia (about 50% of cases) are deficiency of factor V Leiden and prothrombin gene mutation. Other factors favoring thrombosis include protein S and antithrombin deficiencies [20].

Pregnancy and puerperium significantly increases the risk of venous thromboembolism – VTE. It is worth mentioning that it is one of the leading causes of maternal mortality during this period. Risk factors for deep vein thrombosis include age > 40 years, obesity (BMI > 30 kg/m²), a history of venous thromboembolic disease, trauma, prolonged immobilization, malignancy, congenital or acquired thrombophilia, heart failure class NYHA III and IV, Crohn’s disease, ulcerative colitis, nephrotic syndrome, long plane flight, or varicose veins of the lower limbs. Additional risk factors include diagnostic or therapeutic interventions, especially surgery and cesarean section [21].

Due to the high risk of complications the physician should always seek to confirm or exclude the diagnosis of deep vein thrombosis. Among the studies supporting the diagnosis is the measurement of D-dimer in the blood (useless during pregnancy and puerperium) and ultrasound compression test [22, 23]. Diagnosis is based on clinical assessment of the likelihood of thrombosis, such as using the Wells algorithm [24]. However, due to the nature of the symptoms of pregnancy there is an ongoing search for a better algorithm that could help identify or rule out thrombosis in pregnancy. One of these algorithms is described by the acronym LEFt, which stands for changes observed in the left leg (L – left), changes in calf circumference > 2 cm (E – edema), and the emergence of changes in the first trimester of pregnancy (Ft – first trimester) [25]. The presence of one or two/three symptoms was observed in 16 and 58% of women with deep vein thrombosis (DVT – deep vein thrombosis). At the same time lack of any of the symptoms was seen in the absence of thrombosis.

The prevention of relapse of venous thromboembolism – VTE in patients with a history of deep vein thrombosis is a very important task. In most patients, the best choice is a long-term therapy with oral antico-
agulants in a dose adjusted to INR between 2-3. However, in the case of pregnancy due to increased risk of complications for both the mother and the fetus, including teratogenic effects of oral anticoagulants it is preferable to use low molecular weight heparin at a dose adjusted for body weight of the patient and history of thrombosis [26]. Enoxaparin should be used at a dose of 1 mg/kg s.c. every 12 hours or 1.5 mg/kg s.c. every 24 hours, dalteparin at 200 IU/kg s.c. every 24 hours or 100 IU/kg s.c. every 12 hours, and nadroparin dose of 85 IU/kg s.c. every 12 hours or 190 IU/kg s.c. every 24 hours. During treatment, it is recommended to monitor the effectiveness of low molecular weight heparins by monitoring anti-Xa activity. It should be measured 4 hours after the last injection of heparin and should achieve 0.6-1.0 IU/ml or 1.0-1.3 IU/ml heparin, respectively, for use at 12 and 24 hours. Treatment should be continued until birth. Last dose of heparin should be given 24 hours before the planned induction of labor or cesarean section. In the postpartum period, continue taking low molecular weight heparin within the treatment dose and wearing grade II compression stockings.

In his paper Blanco-Molina et al. [27] studied the course of thrombosis and the fate of patients during pregnancy, puerperium or during the use of oral hormonal contraceptives. The study was conducted in Spain, France, Italy, Israel and Brazil. During pregnancy thrombosis occurred in 173 patients, 135 in puerperium, and the 798 during use of hormonal contraception. Patients were tested for thrombophilia, 96, 71 and 479 patients, of which a positive result was obtained, respectively at 55, 42 and 209 Protein S deficiency was found in 5 (5.2%), 5 (7.0%) and 18 (3.8%) women. Patients were then subjected to a three month follow-up, during which the re-thrombosis occurred in the first group of four patients in the second group of six, and in 18 women who originally thrombosis occurred during hormonal oral contraceptives. To rethrombosis occurred in the application of anticoagulant therapy, both with low molecular weight heparin and oral anticoagulants.

Dykes et al. [28] and Goodwin et al. [29] assessed the risk of venous thrombosis in patients with protein S deficiency during pregnancy to 0.1% provided a negative medical history of thrombosis. If the patient has experienced in the past, the risk of thrombosis may reach 22%.

Both presented cases had one thing in common. Patients who had an episode of thrombosis, followed by a detection of thrombophilia. Our task was to reduce the risk of recurrent thrombotic episode, despite the existence of adverse changes in the coagulation profile with which we have to deal with during pregnancy and puerperium. It is worth noting that an increasing number of works is not recommended to use heparin during pregnancy, even in patients with thrombophilia, due to the previously cited concerns about their anticoagulant activity [30, 31]. However, in the case of a history of thrombosis in a patient, the use of anticoagulation is becoming a standard. Not entirely clear is the dose of low molecular weight heparin regimen in pregnancy and puerperium as a part of prevention against recurrence of thrombosis. For women with a history of VTE, ACCP suggests prophylactic dose or medium-dose LMWH, and in some cases only observation.

In the first described clinical situation we had to deal with the patient diagnosed before pregnancy with protein S deficiency. Despite the implementation of low molecular weight heparin treatment in the first pregnancy, there was another incident of thrombosis at puerperium. In the second pregnancy, when the dose was adjusted in response to antifactor Xa activity, we were able to lead the patient through the difficult period of pregnancy and puerperium without thrombotic complications. The key in this pregnancy seems to be adjustment of LMWH dose to increasing body weight and the frequent determination of antifactor Xa, allowing for heparin therapy within therapeutic limits. Without proper monitoring and dose adjustment of LMWH, the scenario of the first pregnancy with the occurrence of thrombosis in the postpartum period could happen again, despite the use of heparin. In both the first and second clinical situation we have observed large blood clots in the placenta, severely limiting the exchange surface between the mother and the fetus. These changes persisted despite the use of higher doses of heparin in second pregnancy.

In the latter case of a patient with antithrombin deficiency, pregnancy and puerperium seemed to be proceeding without any major complications. Throughout the duration of pregnancy normal range of antifactor Xa were observed. However, three situations warrant some attention – dizziness, observed fetal hypotrophy and chest pain in puerperium. Each of these complications can be caused by microclots in the vessels of the brain, placenta and heart, respectively. While the results of laboratory tests and imaging studies (troponin and MRI) in the case of this patients showed no abnormalities, changes in the placenta may indicate its failure caused by thrombosis. Together, the patient's symptoms in pregnancy and detected fetal hypotrophy may suggest that despite appropriate doses of low molecular weight heparin and continuous monitoring of its activity, we
have failed to achieve the full therapeutic effect. This is further confirmed by the findings of thrombotic lesions in histological material taken from the placenta. Changes in the placenta despite the use of heparin were previously described in the work of Skrzypczak et al. [32]. In this paper, it was found that in patients with known thrombophilia and antiphospholipid syndrome, despite the use of heparin, the deposition of fibrin clots and congestion of the placental vascular bed was not avoided. However, serious complications such as pulmonary embolism, stroke, or intrauterine death of a child were avoided. The study which evaluated changes in placenta of pregnant patients, found higher blood clot formation in patients where heparin was used. So what is the effect of heparin in women with congenital or acquired thrombophilia? Increasingly, the question addresses other than antithrombotic effects of heparin. It is known from experiments that heparin promotes the mitosis and proliferation of cytotrophoblast, and the formation of primary syncytiotrophoblast in the villi. It also seems to affect the extinction of inflammation and complement activation in pregnancies with abnormal formation of the placenta [33]. All these changes are designed to improve the exchange surface between the fetus and the mother and gives a chance for survival and normal development of pregnancy, despite a negligible effect on the formation of blood clots in the placenta.

The child developed thrombosis of the lower limb and was finally diagnosed with congenital antithrombin deficiency. Given the seriousness of the complications caused by thrombotic incidents, despite the low observed risk of transmission of AT deficiency from parent to child (<1%), it seems necessary to screen newborns with positive family history of thrombosis. The precipitating factor for thrombosis in the newborn could be parenteral nutrition, dehydration, impaired mobility and, finally, an improper position or too tight diapering.

In summary, all pregnant patients with congenital thrombophilia should make an individual assessment of the risk of thrombosis in order to determine the needed intensity of anticoagulation. You should also inform the patient about all possible symptoms of thrombosis, because despite the use of appropriate treatment its incidence is still high, and rapid intervention could save a patient and her child’s life.

References