CASE REPORT

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A successful outcome of pregnancy in a patient with congenital antithrombin deficiency

Uspešan ishod trudnoće kod bolesnice sa urođenim nedostatkom antitrombina

Mirjana Kovač*, Željko Miković†, Ljiljana Rakičević‡, Snežana Srzentić*, Vesna Mandić†, Valentina Djordjević‡, Dragica Radojković‡

***Blood Transfusion Institute of Serbia,** Hemostasis Department, **Belgrade, Serbia;**
†Gynecology and Obstetrics Clinic "Narodni Front", Belgrade, Serbia;
‡Institute of Molecular Genetics and Genetic Engeeniring, Belgrade, Serbia

Abstract

Background. Presence of inherited thrombophilia is an additional risk factor for maternal thromboembolism and certain adverse pregnancy outcomes, including recurrent fetal loss, placental abruption, intrauterine growth restriction and early-onset severe preeclampsia. Pregnant women with thrombophilia, especially those with antithrombin (AT) deficiency, are at high risk of both kinds of complications. **Case report.** We presented a pregnant women with congenital antithrombin deficiency in the first pregnancy, whose mother had had four times pregnancy-related deep vein thrombosis, and antithrombin deficiency. With the regular laboratory monitoring of hemostatic parameters and gynaecology surveillance including the follow-up of placental vascular flow, the whole pregnancy proceeded without complications. The prophylactic therapy with low molecular weight heparin was introduced from the 20th week of gestation and one dose of substitution therapy with antithrombin concentrate was administrated before delivery. Pregnancy and labour were terminated without complications at the 37th week of gestation, resulting in the delivery of a healthy male newborn of 3.6 kg body weight, 52 cm long, and with the Apgar scores of 9/10. **Conclusion.** A timely made diagnosis of thrombophilia, accompanied with regular obstetrics check-ups and follow-ups of hemostatic parameters during pregnancy, as well as the use of adequate prophylactic and substitution therapy, are the successful tools for the prevention of possible maternal complications and pregnancy itself in our patient with congenital AT deficiency.

Key words:
pregnancy; antithrombin III deficiency; delivery, obstetric; treatment, outcome.

Apstrakt

Uvod. Prisustvo urođene trombofilije predstavlja dodatni faktor rizika od nastanka venskog tromboembolizma u trudnoći, ali i komplikacija same trudnoće kao što su ponavljani gubitak trudnoće, abrupcija placente, intrauterino zaostajanje u rastu i razvoju, te rana preeklampsija. Trudnice sa trombofilijom, a posebno one sa nedostakom antitrombina, u riziku su od nastanka obe vrste komplikacija u trudnoći. **Prikaz bolesnice.** U radu je prikazana trudnica sa urođenim nedostatkom antitrombina u toku njene prve trudnoće, čija majka je četiri puta imala duboke venske tromboze, tokom trudnoće i puerperijuma. Uz redovno laboratorijsko praćenje hemostaznih parametara i redovne akušerske kontrole sa praćenjem važnog parametra placentne vaskularizacije, čitava trudnoća protekla je bez komplikacija. Profilaktička terapija niskomolekularnim heparinom uvedena je od 20. nedelje trudnoće, a supstituciona terapija primenom koncentrata antitrombina, neposredno pre porođaja. Porođaj je protekao bez komplikacija i u 37. nedelji rođena je zdrava muška beba telesne težine 3,6 kg i dužine 52 cm, sa Abgar skorom 9/10. **Zaključak.** Pravovremeno postavljena dijagnoza trombofilije, redovne akušerske kontrole i praćenje hemostaznih parametara u toku trudnoće, kao i primena adekvatne profilaktičke i supstitucione terapije, doprinele su prevenciji mogućih maternalnih ili komplikacija same trudnoće kod bolesnice sa urođenim nedostatkom antitrombina.

Ključne reči:
trudnoća; antitrombin III, nedostatak; porođaj, akušerski; lečenje, ishod.

Introduction

Thromboembolic complication is one of the leading causes of maternal deaths. Pregnant women have an estimated five times increased risk of developing deep venous thrombosis (DVT) compared with non-pregnant women of similar age [1, 2]. The presence of inherited thrombophilia is an additional risk factor for maternal thromboembolism and ad-

Correspondence to: Mirjana Kovač, Blood Transfusion Institute of Serbia, Hemostasis Department, Svetog Save 39, 11 000 Belgrade, Serbia. Phone: +381 11 2455 838, Fax: +381 11 2458 328. E-mail: mkovac008@gmail.com

verse pregnancy outcomes, such as second and third trimester fetal loss, placental abruption, severe intrauterine growth restriction and early-onset severe preeclampsia. Pregnant women with thrombophilia, especially those with antithrombin (AT) deficiency, are at high risk of both kinds of complications [3–5]. Antithrombin deficiency is a rare form of thrombophilia described in 1 of 5,000 individuals. Among afected patients pregnancy is complicated with thromboembolism up to 60% and puerperium up to 33% and adjusted risk (OR) for stillbirth and miscarriage is 5.2 and 1.7, respectively [4]. However, no well-designed clinical studies exist that allow strong recommendations to be made as to how exactly to treat pregnant women with AT deficiency concerning the appropriate dose of low molecular weight heparin (LMWH) and use of substitution therapy with antithrombin concentrate [6].

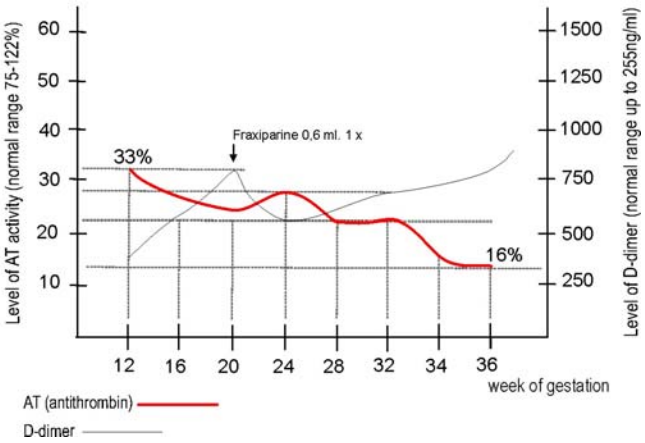

Fig. 1 – The levels of AT and D-dimer during pregnancy

Case report

A patient, 23-year old pregnant woman, was without the history of previous pregnancies and thrombosis, with a positive family history about thrombosis in the first-degree relatives. Her mother had had four times pregnancy-related, deep vein thrombosis, and proved AT deficiency. The first screening for thrombophilia was performed at the 12th week of gestation. A level of AT activity was 33% (normal range 75–122%), demonstrated the AT deficiency. The results of other hemostasis tests were within the reference ranges. The results of protrombin time (PT) of 102%, activated partial thromboplastin time (APTT) of 29.0 s, fibrinogen (3.92 g/L), FVIII (0.89 U), protein C (80%), protein S (75%), APC-R (2.9) and lupus anticoagulant (LA – 1.0) were recorded. The absence of anticardiolipin antibodies (ACA) and mutations of FV Leiden, FII G20210A and MTHFR C677T were obtained. In the further course of pregnancy, the levels of D-dimer and AT activity were monitored, and the values of these parameters were the cornerstone for the planning and application of prophylactic and substitution therapy. At 20th weeks of gestation D-dimer raised up to 694 and 765 ng/mL (referent range 255 ng/mL), and the prophylactic use of LMWH was introduced in doses of 5,700 IU Fraxiparine once a day *sc* After the introduction of anticoagulant therapy the level of D-dimer decreased to 598 ng/mL and the level of AT activity to 28%.

At 32nd weeks of gestation the level of D-dimer was 710 mg/ml, AT 20%, and the significant increase of fibrinogen (5.11 g/l) and FVIII activity (1.8 IU) were recorded. Before delivery, the level of AT dropped to 16% and D-dimer of 774 ng/ml was recorded (Figure 1). These findings were crucial for making the decision to administrate AT concentrate (Kybernine) in a dose of 50 IU/kg/bm. The anticoagulant therapy was stopped 12 hours prior to delivery. The pregnancy was uneventful. The patient was normotensive throughout the whole gestation. Sonographic examinations confirmed eutrophic fetal growth, normal biophysical profile score and normal Doppler indices in feto-placental, fetal and utero-placental blood flows. The pregnancy was terminated without complications at the 37th week of gestation, and resulted in vaginal delivery of a healthy male newborn of 3.6 kg body weight, 52 cm long, and with the Apgar scores of 9/10.

After delivery LMWH was introduced again in the same doses as in the pregnancy, and the second day after delivery, replaced with oral anticoagulant therapy. Normalisation of D-dimer after delivery, with the values dropping from 1,357 on the first day of delivery to 222 ng/mL, 6 weeks following delivery, was crucial for making a decision to stop the anticoagulant therapy 6 weeks after delivery. The levels of fibrinogen and FVIII were normal, too. The AT activity was 43% and confirmed AT deficiency.

In the first week following the infant`s birth, the level of AT in the infant of 66% was recorded. The reference value for the first week of life in healthy full-term infants is 67 ± 13% (according to the Guideline: The investigation and management of neonatal hemostasis and thrombosis. B J Haemat 2002; 119: 295–309). The next control of the infant was performed after one year, and the AT level of 76% was recorded, which was within the reference ranges.

Discussion

Investigation of hemostatic changes during pregnancy, especially natural coagulation inhibitors, showed no significant change of AT activity level, considering gestation age by healthy women without prior complications during pregnancy and without history of thrombosis [7, 8].

In case of the reported 23-year old pregnant woman who had AT deficiency of 33% AT activity in the first trimester, demonstrated by tests for diagnosis of thrombophilia, however, the decrease of AT level during the rest of her pregnancy with the lowest level of only 16% before delivery revealed. That decrease correlated with the increase in clotting factors (significant rise of fibrinogen and FVIII), and elevated levels of D-dimer.

Mc Auley et al. [9] showed similar results in a pregnant woman with thrombosis of superior sagittal sinus in the first trimester of pregnancy, where thrombophilia test showed AT deficiency (37% of normal level 79–136%), and after delivery the activity of AT was 52%. The investigator attributed the reduced level of AT to the acute thrombosis process [9]. Decrease of AT activity and AT antigen, with the lowest level after the delivery was demonstrated by Nelson et al. [10]

after the follow-up of two pregnant women with congenital AT deficiency. The authors emphasized the need to use prophylactic therapy during pregnancy and after delivery, as well as laboratory monitoring during pregnancy, with the fact that plasma AT assay is the most eligible one.

A successful pregnancy outcome in patients with thrombophilia depends on the management, especially in the case of AT deficiency wich is a highly thrombogenic condition [11]. Considering the fact that over 50% of women with AT deficiency developed thrombosis during pregnancy, and that the mother of our patient had four episodes of DVT (the first one during the first pregnancy at the age 22), we introduced prophylactic therapy according to the ACCP recommendation [12]. The prophylactic therapy of LMWH was applied in doses of 5,700 IU Fraxiparine once a day *sc.* from the beginning of the 20th week of gestation, when a significant rise of D-dimer occurred. In the planning of the therapeutical approach in our case, the recommendation concerning prophylactic therapy in pregnancy for AT deficiency patients were considered. Likewise, we considered the facts that she was 23 years old in her first pregnancy, without prior thrombosis and other clinical risk factors such as: hypertension, obesity, diabetes and proteinuria. With regular laboratory monitoring and gynecology surveillance including the follow-up of placental vascular flow, the whole pregnancy proceeded without complications. The extremely low level of AT (16%) before delivery helped in making the decision to introduce one dose of AT concentrate (50 IU/kg/bm) immediately before delivery, resuming anticoagulant therapy after delivery for 6 weeks.

The review of literature showed different approaches in the use of prophylactic and substitution therapy, and each case is very important because of the fact that AT deficiency is a rare form of trombophilia. Kario et al. [13] used AT concentrat in a 22-year old pregnant woman from the 34th gestastion week, three times weekly in doses of 3000 IU. Samson et al. [14] gave AT concentrate for the preparation of the delivery and shortly after delivery, while DeStefano et al. [15] gave only one dose of AT concentrate after delivery. Yamada et al. [16] showed a case of two pregnant women: a 35-year old pregnant patient was given only AT concentrate during pregnancy, while a 22-year old pregnant patient was given only LMWH in prophylactic doses and low doses of aspirin.

Conclusion

A timely made diagnosis of thrombophilia, accompanied with regular obstetrics check-ups and follow-ups of hemostatic parameters during pregnancy, as well as the use of adequate prophylactic and substitution therapy, are successful tools for the prevention of possible maternal complications and pregnancy itself in our patient with congenital AT deficiency.

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