



Antithrombin III Deficiency in Pregnancy

A series of three cases

S Mahdasu and S Alomari



NHS
South Tees
Hospitals
NHS Foundation Trust

Introduction

Hereditary antithrombin deficiency is a thrombogenic disorder associated with a 50–90% lifetime risk of venous thromboembolism (VTE), which is increased during pregnancy and the puerperium in these patients. We present 3 cases of pregnant women with antithrombin (AT) deficiency who presented with a VTE and were treated with LMWH and antithrombin concentrate according to individualised plan.

Case 1

A 31-year-old with Type 1 antithrombin (AT) deficiency (antigen 0.32 U/mL, activity 0.33 U/mL) with a past history of recurrent unprovoked venous thromboembolism (VTE) was switched from warfarin to therapeutic-dose low-molecular-weight heparin (LMWH) when she became pregnant. Her past VTE events included two estrogen-associated VTEs (oral contraceptive pill; ectopic pregnancy and surgery) despite therapeutic warfarin. While on once-daily weight-based LMWH, she developed a new, symptomatic proximal deep vein thrombosis (DVT) at 10 weeks gestation. She was subsequently treated with AT concentrate and LMWH throughout her pregnancy, with no further VTE recurrence and a successful delivery.

Case 2

19 year old primigravida with a known hereditary AT deficiency and history of recurrent first trimester miscarriages, no personal history of thrombosis but a strong family history of AT deficiency and maternal postpartum VTE. The AT activity was 51% and the family history confirmed the diagnosis. She was started on adjusted dose of LMWH tinzaparin 14,000 IU daily from 12 weeks and that was monitored monthly with AT activity and anti Xa level; despite that Xa activity remained subtherapeutic due to heparin resistance and during the last trimester there was a further drop in AT levels. Increasing the LMWH dose actually lowered the AT levels further so the dose of 14,000 IU was resumed throughout pregnancy. AT levels ranged from 33 to 57% during pregnancy; she was delivered by a planned caesarean section at 39 weeks due to breech presentation, the last dose of LMWH was given 24 hours before surgery, 3 hours preoperatively, human AT concentrate infusion was given intravenously. The caesarean section was uneventful and 8 hours post operatively, LMWH was resumed at 4500 IU/day she delivered a healthy small for gestational age male baby weight 2615 grams. AT levels post infusion were 112% at 2 hours and 65% through next day. The AT infusion was planned to be given for 6 days, stopped at day 4 due to allergic reaction and the LMWH dose increased back to 14,000 IU/day; she was discharged on the day 6 post part of the continued to support in 4500IU daily for six weeks

Case 3

G2P1+0, 22 year old with AT deficiency. Her family history was remarkable for AT deficiency in her father and sister. Her father had a history of multiple thrombotic events beginning at the age of 23. At 31 he died from refractory progressive VTE related to small cell carcinoma of the lung. In her past obstetric history 1st pregnancy was uncomplicated. Prior to induction of labour she received LMWH during her pregnancy and post-partum. She also received AT concentrate to maintain AT activity at 80–120% of normal levels. After delivery, she was scheduled to receive prophylactic anticoagulation for 12 weeks post-partum, she discontinued therapy at six weeks. However, she did not experience any thrombotic events.

During her second pregnancy, she was prescribed prophylactic LMWH daily. Despite that she developed a DVT in her right lower extremity at 13 weeks. The DVT extended from the common femoral vein to the popliteal vein. The LMWH dose was increased to therapeutic levels and she received AT concentrate, targeting a peak AT activity of 120%. Despite that she experienced progression of the DVT in her right lower extremity to involve the common femoral vein, popliteal vein, and calf veins. A multidisciplinary decision was made to proceed with IVC filter placement. Anticoagulation management was escalated by the addition of AT concentrate to therapeutic dosing of LMWH. LMWH was discontinued 24 hrs prior to delivery and resumed 12 hrs after delivery. There was no further progression of the DVT, and the baby's vaginal delivery was unremarkable.

Discussion

The high risk of thrombotic events in pregnant patients with hereditary AT deficiency has prompted recommendation from a number of societies such as the (RCOG) and (ACOG) supporting prophylactic LMWH use in hereditary AT deficient patients with a personal or family history of VTE [1,2]. However, patients may still develop VTE despite being on LMWH. In selected patients with previous pregnancy-associated VTE, AT concentrates may be considered for secondary prophylaxis of pregnancy-induced VTE. Pregnant patients with hereditary AT deficiency who develop VTE during pregnancy are often treated with both anticoagulants and AT concentrate. There are no guidelines regarding management of acute VTE in pregnant patients with AT deficiency, and recommendations are based on expert opinion and little data is available on the appropriate timing of initiation, dosing, and duration of AT concentrate during pregnancy and the postpartum period. The two most common indications for AT concentrate in pregnant women with hereditary AT deficiency are for the management of acute VTE during pregnancy despite therapeutic anticoagulation and for prophylaxis in the antepartum, peripartum, and/or postpartum periods. The indication is less clear in women who develop VTE while receiving prophylactic dose anticoagulation, who can potentially be managed by increasing the dose of anticoagulation to therapeutic levels. [1,3-6]

References

1. American College of Obstetricians and Gynecologists Women's Health Care Physicians. ACOG Practice Bulletin No. 138: inherited thrombophilias in pregnancy. Obstetrics and gynecology. 2013;122(3):706–717.
2. RCOG. Reducing the risk of venous thromboembolism during pregnancy and puerperium. RCOG Green-Top Guidelines. 2015;37a.
3. Holbrook A., Schulman S., Witt D. N., et al. Evidence-based management of anticoagulant therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2):e152S–e184S.
4. Bates S. M., Greer I. A., Middeldorp S., Veerstra D. L., Pruthi A.-M., Vandvik P. O. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2012;141(2):e91S–e736S.

5. Bates S. M., Middeldorp S., Rodger M., James A. H., Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. Journal of Thrombosis and Thrombolysis. 2016;41(1):92–128.
6. Kearon C., Akl E. A., Ornelas J., et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315–352.

Correspondence: saboo.al-omari@nhs.net

