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CASE REPORT

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Anticoagulant management in an antithrombin-deficient pregnant woman with a history of venous thromboembolism: a case report

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Abstract

Background Antithrombin deficiency (ATD) in pregnant patients significantly increases the risk of venous thromboembolism (VTE), but guidelines for managing anticoagulation during pregnancy, labour, and postpartum in patients with ATD are limited.

Case presentation A pregnant woman with ATD suffered recurrent VTE in the 20th week of pregnancy despite therapeutic doses of low-molecular-weight heparin (LMWH). The acute VTE was treated with argatroban and then with warfarin until delivery. LMWH with antithrombin (AT) concentrate was introduced before and shortly after delivery, followed by warfarin, which was continued also postpartum. No further complications occurred during the remainder of pregnancy, delivery, and two-year follow-up.

Conclusion Our case highlights the challenges of anticoagulant treatment in pregnant patients with ATD. Standard weight-based LMWH dosing can lead to inadequate anticoagulation, as demonstrated by an acute VTE event in our patient. In our case, the use of argatroban proved to be safe and effective in the acute setting, followed by warfarin in the 2nd and 3rd trimester, and subsequent co-administration of LMWH and AT concentrate before and after delivery. Concomitant use of LMWH and AT concentrate allows for achieving target anti-Xa levels. Measurement of both anti-Xa and AT activity is advisable in this scenario to ensure reliable anticoagulant management. ATD is a heterogeneous disorder; therefore, each successfully managed pregnancy advances clinical practice.

Keywords Anticoagulants, Antithrombin III, Case report, Pregnancy, Venous thromboembolism

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Background

Antithrombin deficiency (ATD) is the most thrombogenic thrombophilia [1]. Those affected have a particularly high risk of venous thromboembolic (VTE) events in situations with a tendency towards hypercoagulability, such as pregnancy (7.3% VTE risk) and postpartum (11.1% VTE risk) [2]. All international guidelines recommend that patients with ATD and previous VTE associated with exogenous oestrogen, pregnancy or unprovoked VTE receive thromboprophylaxis before and after delivery [1]. Low-molecular-weight heparin (LMWH) is the drug of choice as it does not cross the placenta and minimally passes into breast milk. There is no clear consensus on the appropriate starting dose of LMWH, however, for patients who have already been receiving long-term anticoagulation before pregnancy, most guidelines recommend 75% or full therapeutic dose of LMWH. While monitoring the anticoagulant effects of LMWH with an anti-Xa test is not uniformly recommended in pregnant patients with ATD, an anti-Xa test without the addition of exogenous antithrombin (AT) is preferred to avoid overestimating the anticoagulant effect of LMWH in these patients [1]. A peak anti-Xa level of 0.5–1.0 IU/mL is expected with twice-daily administration, while a peak anti-Xa value of over 1.0 IU/mL is expected with once-daily administration [3, 4]. There is no clear recommendation on what to do if the anti-Xa target level is not reached in patients with ATD. In addition, there are no clear guidelines for the treatment of acute VTE during pregnancy in patients with ATD receiving therapeutic doses of LMWH.

In this case report, we present a successfully managed pregnancy and delivery in a woman with severe type I ATD who suffered recurrent VTE during pregnancy despite therapeutic doses of LMWH.

Case presentation

A 35-year-old Caucasian woman with known ATD and a personal history of two VTEs and two previous miscarriages was referred to our hospital during her third pregnancy. Her father and two siblings were known to have ATD and suffered multiple VTEs at a young age. Our patient was first diagnosed with right-sided popliteal venous thrombosis (VT) at the age of 19 while taking combined oral contraceptives. At the age of 21, she suffered a recurrence with an unprovoked ipsilateral VT in the calf, after which she was on prolonged oral anticoagulant treatment with no further VTE recurrences. At the age of 33 her first pregnancy was confirmed and she was switched to therapeutic dose of LMWH. According to our institution's protocol, dalteparin was the LMWH of choice. She suffered a miscarriage in the first trimester, after which LMWH was replaced with warfarin. In the 7th week of her second pregnancy, while on the recommended dalteparin dose (200 IU/kg daily), she suffered a superficial VT of the right calf. Due to her body mass, the exact dose of 200 IU/kg of dalteparin could not be given, so a higher fixed dose (230 IU/kg daily) was used. Three weeks later, she had another miscarriage. When the third pregnancy was confirmed, she was again switched from warfarin to dalteparin at a dose of 230 IU/kg daily. Despite the slightly supratherapeutic dose of LMWH, anti-Xa levels were consistently below the therapeutic range with once-daily administration (1.0–2.0 IU/mL) with a median anti-Xa of 0.59 (0.32–0.75 IU/mL) (Fig. 1).

At 23 weeks of gestation, a left-sided popliteal VT and concomitant pulmonary embolism (PE) occurred. The

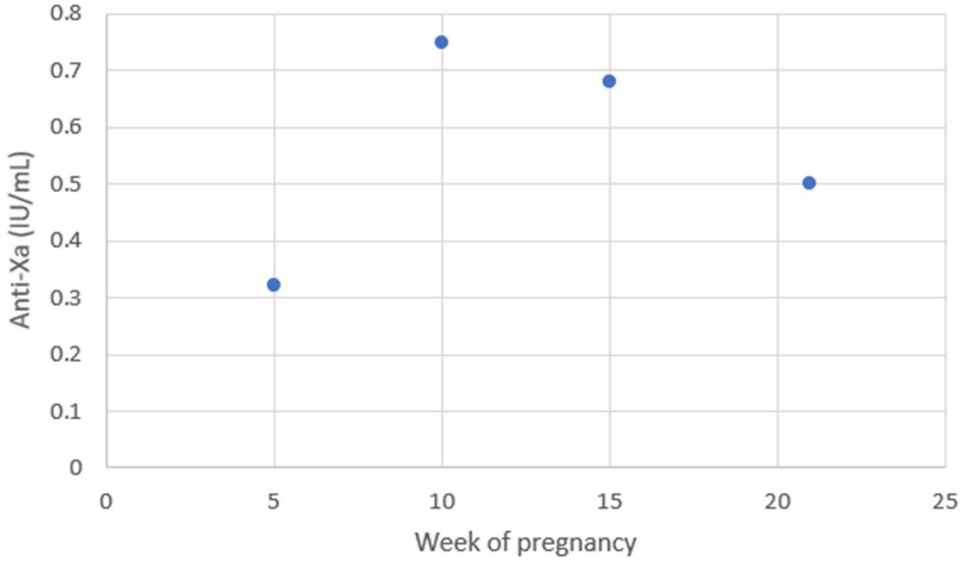


Fig. 1 Anti-Xa levels during pregnancy, while on therapeutic doses of LMWH

PE was classified as intermediate-high risk due to the enlarged right ventricle and elevated NT-proBNP (298 pg/mL) and troponin I (753 ng/L) levels. She was admitted to the intensive care unit (ICU) for observation. As anticoagulation with LMWH was inadequate, she was switched to argatroban, and then to warfarin (target INR 2–3). From the 24th to the 36th week of pregnancy, she was followed-up as an outpatient (time in therapeutic range 63%). No further thrombotic or haemorrhagic complications occurred. In the 36th week of pregnancy, she was hospitalized to prepare her for the planned delivery as close as possible to the due date; warfarin was changed to dalteparin 7,500 IU bid at 69 kg body weight (217 IU/kg daily). In addition, a daily substitution with human AT concentrate (Kybernin, CSL Behring GmbH, Germany) was administered as a slow intravenous infusion over 20 min. The initial AT concentrate dose was calculated according to the manufacturer's instructions and later adjusted to maintain AT activity between 80 and 120%. The trough anti-Xa level measured without addition of exogenous AT (Innovance Heparin, Siemens, Germany) was 0.19 IU/mL (0.13–0.29 IU/mL, median and min to max) and the peak anti-Xa level was 0.61 IU/mL (0.40–0.69 IU/mL). The AT trough activity was 84% (68–93%) and the AT activity ten hours after administration was 111% (102–114%). There was a high linear correlation between AT activity and anti-Xa (Fig. 2).

Labour was induced at 38 completed weeks of gestation with vaginal prostaglandin E2. LMWH was discontinued 18 h before delivery. The vaginal delivery was uneventful with minimal blood loss. The newborn's birth weight was appropriate (3,640 g). LMWH and AT concentrate were reintroduced 12 h after delivery. She was breastfeeding, so warfarin instead of direct oral anticoagulants was re-introduced two days later. AT concentrate was discontinued five days after delivery. LMWH was discontinued when INR was above 2.0 for two consecutive days. At the two-year follow up she was still on warfarin since she continued breastfeeding. No VTE recurrences or haemorrhagic complications occurred. Also, at one year after delivery, no clinical symptoms or signs of post-thrombotic syndrome were detected (Villalta score = 3).

After obtaining approval from the national medical ethics committee, blood samples were collected from our patient, her father and her brother. Detailed genetic and laboratory analyses were performed to better understand the thrombogenic nature of ATD in this family (Fig. 3). In all samples, both AT activity and antigen were decreased, indicating type I ATD. For genetic analysis, DNA was extracted from peripheral blood, and all seven exons and flanking regions of *SERPINC1* were analysed using Sanger sequencing. Genetic analysis revealed a heterozygous missense variant, c.374G > A (p.Gly125Asp), classified as pathogenic according to the guidelines of the American College of Medical Genetics and Genomics. Based on predictions from two in silico tools [5, 6], this substitution may destabilise the conformation of AT, leading to misfolding and intracellular degradation causing type I ATD. Since LMWH binds to AT to exert its anticoagulant effect, lower AT levels can lead to inadequate anticoagulation.

Other thrombophilia defects (factor V Leiden, prothrombin G20210A, protein S and protein C deficiency, and lupus anticoagulants) were not present.

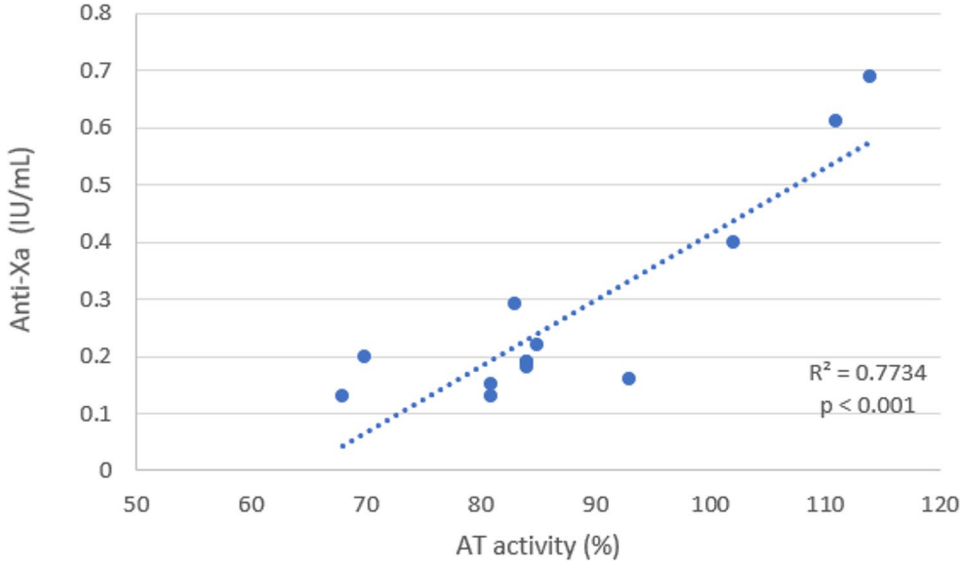
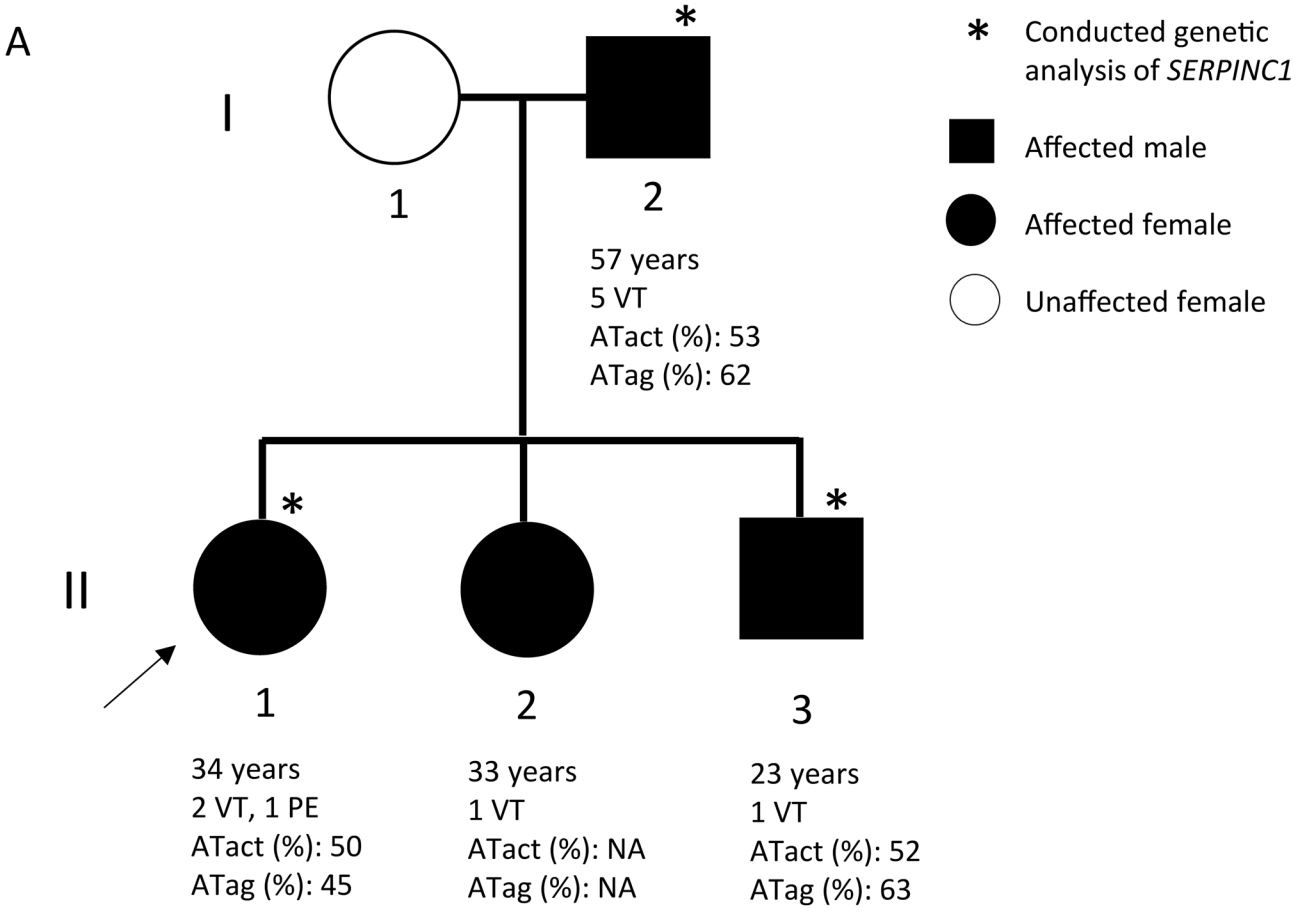


Fig. 2 Correlation between anti-Xa and AT activity



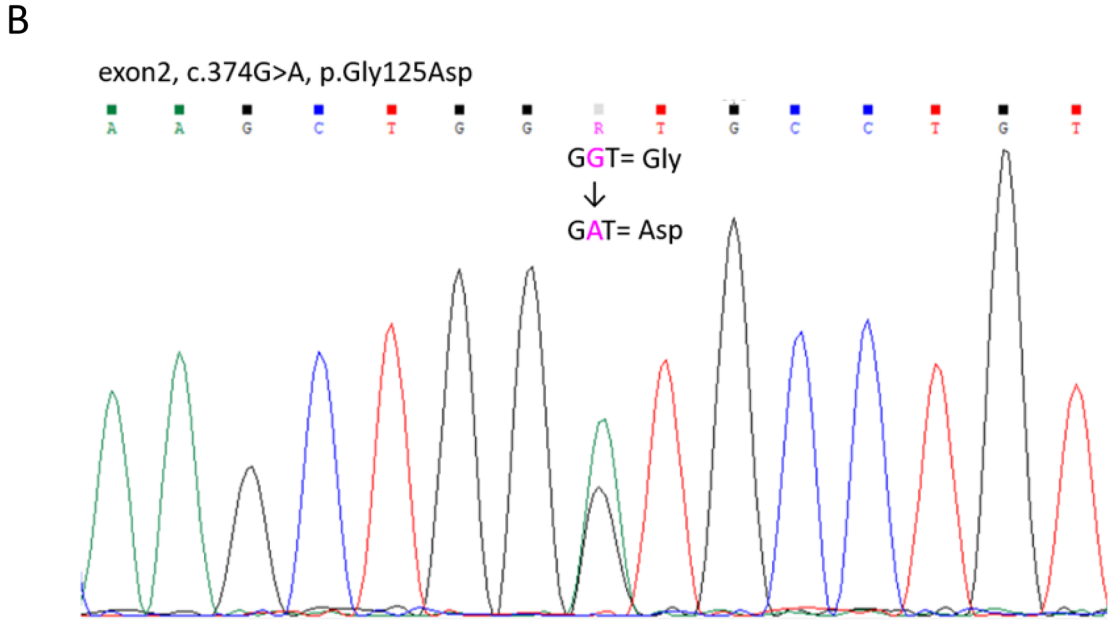


Fig. 3 Laboratory and genetic analysis of the patient and her family. **A** Pedigree and laboratory analysis of our patient (indicated by an arrow) and her family. **B** Genetic variant c.374G>A, p.Gly125Asp in exon 2 of *SERPINC1* identified by Sanger sequencing. Legend: ATact – AT activity, ATag – AT antigen, NA – not available, PE– Pulmonary Embolism, VT – Venous Thrombosis

Discussion

Guidelines for managing ATD in pregnancy are limited, so treatment is still highly individualized, especially in more thrombogenic type I deficiency [1]. Here we present the case of a pregnant woman with type I ATD carrying the rare genetic variant p.Gly125Asp, whose pathogenicity has been confirmed in several reports [7–9].

Our patient suffered a recurrent VTE during pregnancy despite therapeutic doses of LMWH. As there are no firm recommendations for adjusting the LMWH dose based on anti-Xa levels alone, the dose of LMWH was not increased. However, some studies suggest dose adjustment. It was shown in an in vitro study that anti-Xa levels in plasma samples from AT-deficient patients are significantly lower compared with plasma samples from subjects with normal AT activity when spiked with the same doses of LMWH [10]. These results were corroborated in a multicentre case series in women with ATD [11]. The dose of dalteparin required to achieve peak anti-Xa levels (0.5–1.0 IU/mL) was the highest among different LMWHs and was on average 100% higher than recommended by the manufacturer. Usefulness of LMWH therapy monitoring with anti-Xa is controversial, because there are cases without VTE despite subtherapeutic anti-Xa levels [12], as well as cases with VTE despite desirable anti-Xa levels [11]. As bleeding is rare in pregnant patients with ATD and treatment aims to reduce the risk of VTE, measuring trough rather than peak anti-Xa may better reflect appropriate anticoagulation. Currently there are no evidence-based desired trough anti-Xa levels, but levels above 0.1 IU/mL have been suggested [11].

There is little guidance on how to proceed when a pregnant patient with ATD develops a VTE while on therapeutic doses of LMWH. Expert consensus supports the concomitant use of an AT concentrate with LMWH [13]. However, our patient presented with an intermediate-high risk PE, requiring immediate ICU admission. Argatroban was chosen due to its direct thrombin inhibition [14], immediate effect, greater availability in our ICU, and the broader experience of emergency physicians with it compared to the more specialized use of AT concentrate. Additionally, argatroban offers simpler monitoring by measuring activated partial thromboplastin time, while AT concentrate requires careful monitoring and dosing adjustments, which can be challenging in an acute setting. Argatroban has already been used successfully in pregnancy for heparin-induced thrombocytopenia [15], including in a pregnant woman with ATD [16]. However, to our knowledge, this is the first documented use of argatroban in a pregnant woman with ATD outside this setting.

Post-treatment of VTE with LMWH and AT concentrate would have required a long hospital stay for our patient, so warfarin was preferred. This decision was based on the negligible risk of warfarin-induced fetopathy from the second trimester onwards and the positive experience with the safe use of warfarin in pregnant women with artificial heart valves [17]. It is important to note that there are risks associated with warfarin use beyond the first trimester in pregnancy, such as fetal or neonatal intracranial haemorrhage [18]. These risks were explained to the patient, and she agreed to proceed with warfarin therapy. Our patient was closely monitored by our anticoagulation and obstetric teams. This allowed for a good time in therapeutic range and an uneventful pregnancy until 36 weeks gestation when hospital admission was scheduled. After switching to LMWH and AT concentrate the target peak anti-Xa level was achieved. Despite the high correlation observed between anti-Xa levels and AT activity, monitoring both is crucial to minimize the risk of thrombotic events due to inadequate anticoagulation as a result of low AT activity and to prevent bleeding complications once AT levels have normalized. However, further information on the relationship between LMWH dose, anti-Xa levels and anticoagulant effect might improve the management of these patients with LMWH.

Conclusions

In conclusion, weight-based LMWH dosing may not provide adequate anticoagulation in pregnant patients with ATD, as shown by an acute VTE in our patient. Argatroban proved to be an effective and safe alternative anticoagulant for treating acute VTE in such patients. If using LMWH, concomitant use of AT concentrate allows for achieving desirable peak anti-Xa levels. In this situation, both AT activity and anti-Xa monitoring are required for reliable treatment with LMWH. ATD is rare and has a very heterogeneous clinical picture depending on the genetic variant. Therefore, each successfully managed pregnancy, as described here, contributes to better and standardized clinical practice.

Abbreviations

ATD	Antithrombin deficiency
VTE	Venous thromboembolism
LMWH	Low–molecular–weight heparin
AT	Antithrombin
VT	Venous thrombosis
PE	Pulmonary embolism
ICU	Intensive care unit
ATact	AT activity
ATag	AT antigen

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Authors' contributions

MK, TVC, TR and MBM have made substantial contributions to the design of the work. MK obtained the informed consents. MK, TVC, ML, MM and GT contributed to the clinical data acquisition. TR performed all the genetic

analysis. MBM and TR compiled all the laboratory data. MK, TVC and TR prepared a draft. All the authors revised the manuscript and approved the submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was conducted in compliance with the Declaration of Helsinki, and an approval was obtained from the Medical Ethics Committee of the Republic of Slovenia.

Consent for publication
The patient provided written informed consent for the publication of information about herself and her family.

Competing interests
The authors declare no potential competing interests.

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