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Apixaban therapy in a pregnant woman with heparin-induced thrombocytopenia and venous thromboembolic events caused by congenital antithrombin deficiency: A case report

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ABSTRACT

We report the case of a 35-year-old pregnant woman (gravida 3, para 1) with antithrombin deficiency who was successfully treated with apixaban. She had a history of heparin-induced thrombocytopenia and venous thromboembolic events. Pregnancy was confirmed while the patient was having anticoagulant therapy for a persistent thrombus. Choice of anticoagulation during her pregnancy was limited because of her antithrombin deficiency: heparin was not an option because of her history of heparin-induced thrombocytopenia; antithrombin-dependent anticoagulant drugs were not an option because of her antithrombin deficiency, and she preferred outpatient management. Despite the fact that there are no reports of its use in pregnant women, we selected apixaban (10 mg/day), a direct Xa inhibitor, as the best solution. No progression of thrombus was noted during the pregnancy. The newborn baby had no external congenital anomalies, intracranial hemorrhage, or bleeding tendency. Thus, apixaban may be a candidate for anticoagulant therapy in pregnant women with a history of venous thromboembolic events and heparin-induced thrombocytopenia.

1. Introduction

Pregnant women are at higher risk for venous thromboembolism than women who are not pregnant. The incidence of pregnancy-related venous thromboembolism is 1.72 per 1000 deliveries [1].

Antithrombin (AT)-independent anticoagulant drugs such as thrombin inhibitors and direct Xa anticoagulants are necessary to treat pregnant women with preexisting venous thromboembolic events (VTE), history of heparin-induced thrombocytopenia (HIT) and underlying congenital antithrombin deficiency. Apixaban is a highly selective direct Xa oral anticoagulant that has been used prophylactically in recent years for the treatment of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE). However, because apixaban is a new drug, the risks to the fetus (*via* the placenta), such as teratogenicity and bleeding events, remain unknown. Although several studies have reported the use of direct thrombin inhibitors such as fondaparinux and danaparoid in pregnant women, there have been no studies on the use of apixaban in pregnant women.

Here, we report the successful use of apixaban in a pregnant woman who had congenital AT deficiency-induced VTE and was not a candidate for anticoagulant therapy with heparin because of HIT. The CARE guidelines were followed for this case report.

2. Case Presentation

A 35-year-old woman (gravida 3, para 1) was referred to the hospital with a history of HIT and VTE in early pregnancy. Her first baby was born vaginally at 41 weeks of gestation eight years prior. The day after delivery, she experienced pain in her lower limbs and was diagnosed with DVT and PE. Under anticoagulant therapy with warfarin, she fully recovered 6 months later and then finished anticoagulant treatment. In her second pregnancy (one year prior), DVT and PE recurred at 8 weeks of gestation. After the cause of her thrombotic predisposition was identified, she was diagnosed with congenital AT deficiency by virtue of AT activity 37% (normal range 80–120%). She had no relevant family history of antithrombin deficiency. At the beginning of treatment with a subcutaneous infusion of heparin calcium (30,000 U/day), she experienced a dramatic decrease in her platelet count (min 93,000/μL) and an increase in her liver enzyme levels (max aspartate aminotransferase, 54 U/L [normal range 12–35 U/L]; alanine aminotransferase,

Abbreviations: AT, antithrombin; VTE, venous thromboembolic events; HIT, heparin-induced thrombocytopenia; DVT, deep vein thrombosis; PE, pulmonary embolism; FDA, Food and Drug Administration; DOAC, direct-acting anticoagulant.

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75 U/L [normal range 6–31 U/L]). She was diagnosed as having HIT type II (anti-heparin-platelet factor 4 conjugate antibody 0.8 U/mL [normal value under 1.0 U/mL], platelet count min 93,000/μL, 6 days after heparin administration). It was thought that it would be difficult for her to continue pregnancy, and she underwent a therapeutic abortion at 10 weeks of gestation. After delivery, her treatment was restarted using direct oral anticoagulants (DOACs), followed by warfarin for maintenance therapy. Nevertheless, a thrombus remained in her right pulmonary artery and left soleus muscle vein.

Her current pregnancy was confirmed while she was under anticoagulant therapy for the remaining thrombus. She was referred to the Tertiary Perinatal Medical Center again at 4 weeks of gestation. Because the patient had a history of DVT exacerbation associated with HIT, continuing her pregnancy was considered difficult in the context of contraindications for the use of heparin. However, as the patient strongly wished to continue her pregnancy, we decided to administer apixaban (10 mg/day), after obtaining her written informed consent. We considered using warfarin after 10 weeks; however, warfarin was listed as grade D by the Food and Drug Administration (FDA) for pregnant women. We chose apixaban, which is FDA grade B. At this point, an organized thrombus was confirmed in her leg veins on ultrasonography of the lower extremities. Ultrasonography was performed periodically until delivery; however, no exacerbation of the thrombus was noted. Contrast-enhanced chest computed tomography conducted at 36 weeks of gestation revealed no findings suggestive of thrombus in the pulmonary blood vessels.

Because fetal growth was normal, a planned delivery was induced at 38 weeks of gestation using oxytocin. Apixaban was discontinued 48 h before labor induction, and argatroban (0.7 μg/kg/min) and an AT drug (15,000 U/day) were both administered intravenously as an alternative anticoagulant therapy. She delivered a healthy infant 8 h after labor induction. The baby was female, with a birth weight of 2932 g and Apgar scores of 8 and 9 at 1 and 5 min, respectively. The intrapartum blood loss was 625 mL. The baby had no external anomalies, intracranial hemorrhage, or bleeding tendency. We checked neonatal coagulation parameters after about 2 months later. The baby's PT-INR was 1.0% (normal range 0.86–1.22%), APTT was 31.5 s (normal range 35.1–46.3 s), fibrinogen was 162 mg/dL (normal range 82–383 mg/dL) After delivery, the patient took warfarin (4.5 mg/day) to prevent VTE and has been following an uneventful course, without any recurrence for about 1 year.

Written informed consent was obtained from the patient for the publication of this case report. Publication was also approved by the Toho University Omori Medical Center Ethics Committee (M17224).

3. Discussion

This case report may provide limited evidence for the use of oral medications to replace warfarin. Because the patient had experienced VTE caused by her congenital AT deficiency and was not a candidate for anticoagulant therapy with heparin because of a history of HIT, the options for anticoagulant therapy were extremely limited.

In general, anticoagulant therapy options are limited to pregnant women. As unfractionated heparin and low-molecular-weight heparin cannot be transmitted through the placenta and will not increase bleeding and teratogenic risks, they are considered to be the first choice of treatment [2,3]. However, when HIT occurs with the use of heparin, as in the present case, alternative therapy with another anticoagulant drug is necessary. As alternative medications, fondaparinux and danaparoid have been used in pregnant women and are considered highly safe [4]. Fondaparinux binds to antithrombin and indirectly inhibits the Xa factor. It is the most widely used alternative drug to heparin in pregnant women with a history of HIT [4,5]. Danaparoid is a low-molecular-weight heparinoid and is considered safe for pregnant women because of a lack of placental transmission [6]. However, because both drugs can only exert an anticoagulant effect in the presence of AT, they cannot be fully effective in patients with congenital AT deficiency, as in the present case.

Argatroban is the most reasonable drug in cases similar to the present case, in that it can demonstrate an anticoagulant effect without involving AT. However, because of its short half-life (<1 h), argatroban must be administered parenterally and therefore is not suitable for

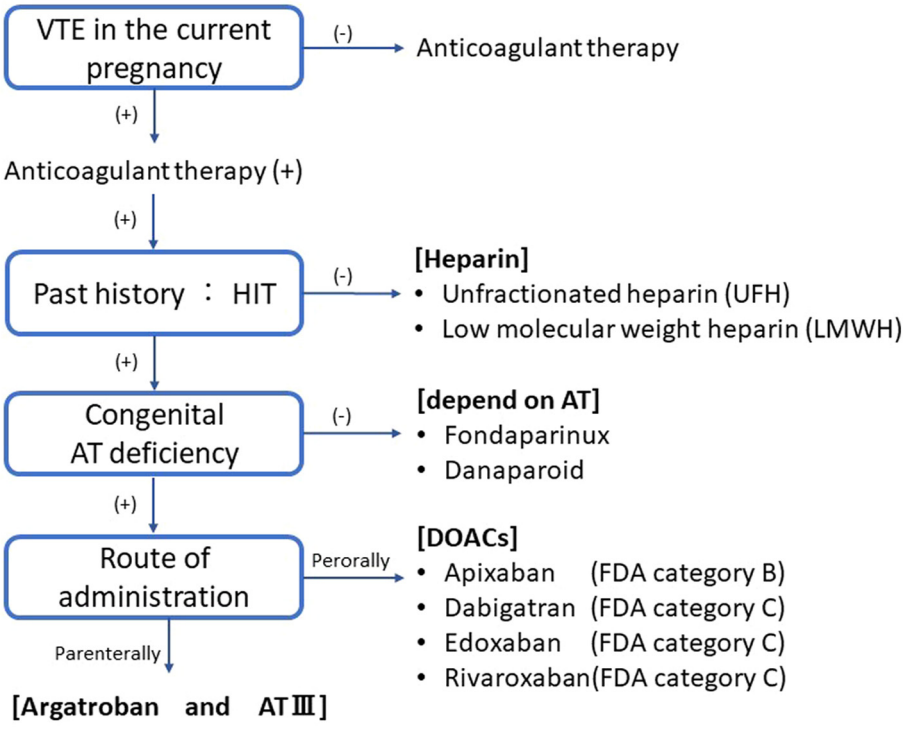

Fig. 1. Treatment strategy in this case.

long-term outpatient management. Ideal anticoagulant therapy is one that (i) is quickly responsive, (ii) has stable pharmacokinetics and drug metabolism, (iii) has few interactions, (iv) needs little periodical monitoring, and (v) can be administered orally. DOACs were developed to meet these requirements. Apixaban, dabigatran, edoxaban, and rivaroxaban are representative DOACs that are available in Japan. Among these drugs, apixaban has a lower bleeding event risk at the time of treatment for acute VTE than the other two drugs [7] and was classified as FDA category B at that time [8]; hence, we chose apixaban to treat VTE in the present case (Fig. 1).

After admission for delivery induction, argatroban was switched to a drug with a shorter half-life, and drug administration was discontinued just before delivery to ensure both the prevention of VTE and a reduction in the bleeding risk during delivery. Although apixaban induced no adverse events in the mother or fetus in the present case, a previous study suggested that apixaban may increase the risk to the fetus. Bapat et al. examined the transmission ability of the human placenta using apixaban [9]. The fetal blood concentration of apixaban *in vivo* was estimated as 30–50% of that in maternal blood. On the basis of the fact that fetal serum has a low coagulation ability, Bapat et al. suggested that the incidence of fetal or neonatal complications may increase with apixaban from a physiological point of view [9]. Therefore, a limitation of the present case report is that an increased risk of fetal or neonatal neurodevelopmental complications cannot be ruled out.

In conclusion, we found that apixaban may be safe and effective for the treatment of pregnant women with preexisting VTE and a history of HIT. Further studies are needed to accumulate sufficient data to verify apixaban as an alternative option for anticoagulant therapy during pregnancy.

Contributors

All authors made a substantive contribution to the information or material submitted for publication.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient Consent

The patient provided informed consent, and the study design was approved by the appropriate ethics review board.

Provenance and Peer Review

This case report was peer reviewed.

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