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CASE REPORT

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Heparin induced thrombocytopenia in pregnancy: A therapeutic challenge case report and literature review

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Abstract

The anticoagulants of choice for the prevention and treatment of venous thromboembolic disease during pregnancy are unfractionated heparin and low-molecular-weight heparin. Heparin-induced thrombocytopenia (HIT) is introduced as a rare but critical side effect of heparin products raising the thromboembolic event paradoxically. Here, we present a case of HIT in pregnancy with challenging management due to coincidence of lupus anticoagulant (LA) and limited anticoagulant options in the pharmaceutical market of our country of residence. We describe a 6-week pregnant patient with deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE), which developed HIT during antenatal care. Therapeutic anticoagulation was initiated with argatroban, then switched to apixaban due to limited access to argatroban. Another therapeutic challenge was the concurrent incidence of LA. The interdisciplinary care team decided on adding up warfarin and scheduled termination at 12 weeks regarding the hazardous condition of the patient. We also reviewed related case literature to convey a new insight into managing pregnancy-related HIT. HIT is a pro-coagulatory and lethal complication associated with heparin therapy that can be diagnosed by clinical suspicion, the 4T score system, and confirmatory laboratory analyses. Alternative anticoagulation is the cornerstone of the treatment and an interdisciplinary plan will be worthwhile to make the best clinical decision regarding the critical situation and least the thromboembolic events mortality during pregnancy.

KEYWORDS

anticoagulation, apixaban, argatroban, case report, heparin-induced thrombocytopenia, lupus anticoagulant, pregnancy

1 | INTRODUCTION

Heparin-induced thrombocytopenia (HIT) accounts as an adverse effect of anticoagulation treatment particularly associated with unfractionated heparin and low molecular weight heparin including enoxaparin. HIT occurs in approximately 0.3%–3% of patients characterized by slightly low platelets counts and an increased tendency of thromboembolism events by over 50% of untreated patients. As the pathogenesis, the antibody formation against the

complex heparin/platelet factor 4 (PF4) and then acting with Fcγ RIIa causes the activation of platelets and endothelial which result in manifestation of HIT.[1,2] Although the incidence of HIT in pregnancy is rare (1.72 per 1000), its diagnosis and treatment are vitally important due to the increased risk associated with thromboembolism. The neglected gradual decrease in the platelet count during hospitalization, which heralds HIT in a patient under anticoagulation therapy, may be assigned to a diagnostic challenge in pregnancy-related HIT. The following challenge is the treatment approach for pregnancy-related HIT because of the hypercoagulation state linked to pregnancy, the underlying diseases predisposing to thrombosis such as antiphospholipid syndrome (APS) or lupus anticoagulant (LA), and the contraindication to using alternative agents make the clinicians very limited in patient management.[3] Here, we report a 6-week pregnant woman suffering from both LA and HIT in pregnancy, which was a diagnostic and therapeutic challenge for us due to the simultaneity of her conditions and the limitation in the availability and access to the administration of novel oral anticoagulants (NOACs) agents which makes our case a rare and not well defined case.

2 | CASE PRESENTATION

A 36 years old female at 6 week of gestation was hospitalized because of severe dyspnea. History did not suggest a significant problem, except for the in vitro fertilization (IVF) in the current pregnancy, an abortion, and a cesarean. At admission time, she was considered to assess by gestational ultrasonography and transthoracic echocardiography immediately. Echocardiography indicated the right ventricle dilatation accompanied by prominent dyspnea and low oxygen saturation. However, the Doppler ultrasound of the lower extremity for deep venous thrombosis (DVT) diagnosis did not report any clot or abnormality. Performed computed tomography pulmonary angiogram (CTPA) showed a massive plus subsegmental pulmonary thromboembolism (PTE) and a high troponin titer in laboratory exams. After admission to the critical care unit, she received the treatment dosage of unfractionated heparin 5000 units bolus intravenously followed by 1500 units/h, and Alteplase 100 mg intravenous infused over 2 h, considering not uprising the saturation and massiveness of the PTE. After anticoagulation with heparin, she was discharged while being stable and prescribed subcutaneous enoxaparin. One week later, she returned with the presentation of exacerbated dyspnea and severe unilateral calf pain, which was consonant with DVT, proven by Doppler ultrasound. Laboratory findings also indicated a low platelet count (43×10^9/L) with more than 50% reduction from baseline (225×10^9/L). The 4T score criteria assessment (6 of maximum 8 scores) and history of receiving heparin/enoxaparin during the last 13 days established the diagnosis of HIT. Heparin was discontinued immediately, and she was started on argatroban intravenously at 2 mcg/kg/min infusion. Regrettably, with limited access to argatroban (the patient received argatroban only for 2 days), we had to start apixaban 10 mg orally twice a day. A presumed hypercoagulation state, and the history of earlier abortion indicated the APS/LA panel tests which were obtained just before the initiation of apixaban. PTT-LA (65.9 s), DRVVTs (159.4 s), and DRVVTc (121.5 s) compared to normal were high, while B2 Glycoprotein (IgM and IgG) and anti-Smith antibodies reported negative. Some genetic thrombophilic disorders were also evaluated, including factor V Leiden mutation, protein C and S deficiency, and prothrombin G20210A mutation which were all negative. This pattern suggested a pro-coagulatory state linked to LA. Given the heparin contraindication, limited availability to argatroban, and the fact that Vitamin K antagonists are highly recommended in HIT, we thought to try out oral warfarin (after platelet count rises to normal range) to prevent LA-associated thrombotic events after hematologist consult. She ultimately was prepared for scheduled termination at 12 weeks by the obstetrician's opinion regarding the hazardous situation of the patient. Oral anticoagulation with warfarin and apixaban was stopped 24–48 h before termination, which allowed for achieving normal INR on the procedure day, and continued after the operation. The patient was discharged in a good condition with relief of her symptoms. We followed up with the patient after pregnancy termination and she has been doing well, with no reported adverse events.

3 | DISCUSSION

Although the incidence of HIT in pregnancy is insignificant, it can become a real challenge in management if it happens. Specifically, this challenge may be highlighted when the treatment options are restricted due to limited availability or being teratogen for the fetus.[4] In this case, the complicated gestation with venous thromboembolism (VTE) accompanied by a hypercoagulation state of LA and HIT made a challenge in decision-making regarding the limited access to argatroban and constrained administration of apixaban and warfarin during pregnancy; finally, we considered termination for this patient. Besides managing pregnancy-related HIT, timely diagnosis associated with the gradual decrease in platelet count and clinical suspicion should be enhanced.[5] 4T score is an acknowledged diagnostic criterion for

HIT cases which consists of both clinical and laboratory diagnostic tools, estimating the incidence probability of HIT concerning the severity of thrombocytopenia, thrombosis occurrence, and elapsed time since receiving heparin.[6] According to the 4T score assessment, this standpoint might be proposed that the gradual drop of platelets (during days 5 to 10 of receiving heparin or heparin therapy within the last 30 days) either during hospitalization or at the time of discharge in the patient under heparin therapy should strengthen the clinical suspicion to HIT.[6] However, the decreasing trend of the patient's platelet at discharge time was ignored in our case, although the platelet count was normal. Addressing the HIT and pregnancy-associated thrombophilia conditions stands on NOACs administration and platelets monitoring. NOACs consist the treatment of choice for the thrombotic state associated with HIT via inhibiting the coagulation factors IIa and Xa.[7,8] We conducted a literature review explaining the diagnostic and management features of HIT occurring in pregnancy. Searching, screening, and extracting data were performed in PUBMED, Google Scholar, and Embase focusing on only English language papers published between 2000 and 2023. Finally, 12 included studies were selected based on diagnosis and management of the current newly onset HIT (without prior history of HIT), which was reported in the paper. The most thromboembolic events in the included studies suggested DVT (41.6%, 2/3 in the first trimester and 1/3 in the second/third trimesters) and PTE (50%, 1/2 in the first trimester and 1/2 in the second/third trimesters) (Table 1). Three studies addressed the management of HIT and associated thrombotic events in valvular heart problems. Other thrombophilia conditions related to HIT following heparin administration were portal vein thrombosis, cerebral venous thrombosis, severe congestive heart failure, and maternal-fetal morbidity. Eleven studies (91.6%) of the included articles suggested the NOACs therapy for managing pregnancy-related HIT, one study considered danaparoid therapy (without NOACs), and one suggested the combination of danaparoid plus lepirudin. The administration of oral warfarin was reported in five articles (41.6%). Most studies (41.6%) indicated the benefits of Xa factor inhibitor Fondaparinux (Table 1). Subcutaneous Fondaparinux 2.5 mg/day or 7.5 mg/day either for prophylaxis or treatment application was suggested for HIT in pregnancy (with the target of anti-Xa activity of >0.25 mg/L and discontinued 24–36 h before induction).[1,8] Lepirudin or r-hirudin (in 33.3% of included studies) also had application as a choice of NOAC category to treat HIT in pregnancy. Huhle et al. administrated Lepirudin in a dosage of 15 mg twice a day subcutaneously. After delivery, Lepirudin would be increased to adjust the APTT 2–2.5 times the control, and the patient was treated for 3 weeks on the desired dose.[9] Lepirudin also was injected intravenously at the dose of 0.15 mg/kg/h then switched to subcutaneous form 1 mg/kg every 8 h.[4] HIT was diagnosed during the second visit to our clinic, and she was treated with argatroban (in 33.3% of included studies) intravenously as a direct and highly selective thrombin inhibitor agent. Unlike fondaparinux, argatroban can be canceled or continued during induced labor (2.5 μg/kg/min to achieve APTT with 1.5–2.0 times control).[7,8] The initial dose of argatroban could be ranged from 0.7 to 8 μg/kg depending on the patient setting and clinician decision based on the included studies.[10,11] However, despite the benefits of argatroban in the treatment of HIT, it may be scarcely available in many countries. Therefore, due to the limited access to argatroban, the treatment course was continued with oral apixaban. Apixaban is a highly selective direct Xa oral anticoagulant that has been used prophylactically in recent years for the treatment of VTE, including DVT and PTE. Moreover, the administration of oral apixaban 10 mg/day plus argatroban in identified HIT patients has been approved. However, 48 h before induction, discontinuation of apixaban and resuming argatroban infusion have been recommended.[3] Subcutaneous danaparoid also was considered in pregnancy-related HIT, but regarding the limited availability in many countries, it has not been widely utilized in included studies. Danaparoid could be administrated with or without NOAC in patients with former diagnosed HIT or newly-onset HIT.[12–14] The coexistence of hypercoagulation state such including LA and HIT made us face limitations in NOACs administration. European Alliance of Associations for Rheumatology (EULAR) did not recommend the NOACs therapy with factor Xa inhibition in the APS because of the high risk of recurrent thrombosis.[15] Contrariwise, another opinion has confirmed the use of NOAC in cases with venous thrombosis or having single/double anti-phospholipid antibodies.[16] Therefore, the controversy in utilizing NOACs in the APS/LA treatment was challenging to the decision. Warfarin is a highly recommended alternative option for the treatment of APS/LA; however, its fetal teratogenicity in pregnancy seriously restricts its use.[15] Concerning the venturous condition of the patient and the high recommendation level of evidence in utilizing warfarin for APS/LA-related thrombophilia prevention, oral warfarin was added to the treatment course after the obstetrician and hematologist consultation. The teratogenic effect of warfarin has confined its administration, preferably after the first trimester or after delivery, if indicated (to achieve INR = 2.5 or ×2 normal).[7,8,17] On account of the complicated pregnancy caused by the

TABLE 1 Alternative anticoagulation therapy in heparin-induced thrombocytopenia.

Ref	Patient	Past/Present History	Management before HIT diagnosis	Lab findings	Management after HIT diagnosis
[17]	26 year old, 7 weeks	PTE, DVT	Heparin Tinzaparin	Plt: 150×10^9/L PF4/Hep Ab Positive	Lepirudin Warfarin (at 15 weeks and postpartum) Cesarean (at 38 weeks)
[7]	33 year old, 7 weeks	DVT	Heparin Urokinase AT concentrate	Plt: 21×10^9/L Low AT activity 4T[b]: 6/8 PF4/Hep Ab Positive	Argatroban Fondaparinux (at 24 weeks) AT concentrate NVD (at 37 weeks) Warfarin (postpartum)
[8]	38 year old, 10 weeks, G1P0	Hyperemesis gravidarum Weight loss	Heparin	Plt: 50×10^9/L PF4/Hep Ab Positive	Argatroban Fondaparinux NVD (at 38 weeks) Warfarin (postpartum) plus Fondaparinux (postpartum)
[18]	34 year old, 10 weeks	PTE, DVT	Heparin TPA[a]	Plt: 46×10^9/L PF4/Hep Ab Positive	Lepirudin (at 10 weeks) Acenocoumarol (at 12 weeks) Danaparoid (at 34 weeks) Cesarean (at 35 weeks)
[1]	29 year old, 27 weeks G3P2	CHF[c] (NYHA IV) Severe MR[d] Oligohydramnios Placental insufficiency IUGR[e]	Heparin	Plt: 121×10^9/L 4T: 6/8 PF4/Hep Ab Positive	Fondaparinux Aspirin Cesarean (at 32 weeks)
[12]	29 year old, 5 weeks	Tricuspid valve replacement surgery treated with Phenprocoumon	Heparin	Plt: 143×10^9/L PF4/Hep Ab Positive	Danaparoid Cesarean (at 37 weeks, following preeclampsia) Phenprocoumon (after cesarean)
	37 year old, 5 weeks	Mitral Valve Stenosis treated with Phenprocoumon	Heparin	Plt: 109×10^9/L PF4/Hep Ab Positive	Danaparoid Cesarean (at 33 weeks, following cardiac insufficiency) Phenprocoumon (after cesarean)
[19]	24 year old, 34 weeks	PTE	Heparin Enoxaparin	Plt: 44×10^9/L PF4/Hep Ab Positive	Fondaparinux Cesarean (at 37 weeks)
[9]	21 year old, 25 weeks	History of SLE[f] and recurrent VTE, under immunosuppressive therapy and Phenprocoumon PTE, DVT	Dalteparin	Plt: 59×10^9/L PF4/Hep Ab Positive	Lepirudin Cesarean Phenprocoumon (after cesarean)

TABLE 1 (Continued)

Ref	Patient	Past/Present History	Management before HIT diagnosis	Lab findings	Management after HIT diagnosis
[20]	39 year old, 25 weeks	PTE, DVT	Enoxaparin	Plt: 50×10^9/L PF4/Hep Ab Positive	emergency pulmonary embolectomy under CPB[g] using Tirofiban and heparin throughout the surgery Fondaparinux NVD (at 38 weeks) Warfarin (postpartum)
[10]	26 year old, 33 weeks G1P0	PVT[h]	Enoxaparin	Plt: 37×10^9/L PF4/Hep Ab Positive	Argatroban NVD (at 39 weeks)
[11]	33 year old	Mechanical prosthetic valve treated with Warfarin	Heparin TPA	PF4/Hep Ab Positive	Argatroban MVR[i]
[4]	27 year old, 8 weeks	Cerebral VT[j] PTE	Heparin Enoxaparin	Plt: 111×10^9/L PF4/Hep Ab Positive	Lepirudin Warfarin (at 14 weeks) Cesarean (at 36 weeks)

[a]Tissue Plasminogen Activator.
[b]4T score.
[c]Congestive heart failure.
[d]Mitral regurgitation.
[e]Intrauterine growth restriction.
[f]Systemic lupus erythematosus.
[g]Cardiopulmonary bypass.
[h]Portal vein thrombosis.
[i]Mitral valve replacement.
[j]Venous thrombosis.

hypercoagulation state and limited treatment options, we had to use warfarin in the first trimester. Ultimately, the termination schedule was considered. Before the safe termination or induction that would be processed by proper anesthesia, a variously long drug-free interval should be considered (depending on the anti-coagulant agent). These intervals must be paid attention to when planning delivery.[1] We highly emphasized the multidisciplinary team consists of hematologists, obstetricians, and anesthesiologists to determine the plan for termination/induction (or surgery if needed) and the mode of delivery, assigning drug-free intervals, monitoring the anticoagulation activity, and consider evidence-based to handle the patient with the diagnosis of HIT.[21]

4 | CONCLUSION

Heparin-induced thrombocytopenia is a pro-coagulatory and lethal complication associated with heparin therapy that can be diagnosed by clinical suspicion, the 4T score system, and confirmatory laboratory analyses. Alternative anticoagulation with NOAC agents instead of unfractionated heparin or low-molecular-weight heparin is the cornerstone of the treatment. An interdisciplinary plan will be worthwhile to make the best clinical decision regarding the critical situation and least the thromboembolic event mortality.

AUTHOR CONTRIBUTIONS

Seyyed Mojtaba Nekooghadam: Data curation; investigation; resources; supervision; validation. **Sepehr Ebrahimi-Dehkordi:** Writing – original draft. **Elham Paraandavaji:** Data curation; investigation. **Mehdi Pishgahi:** Conceptualization; data curation; resources. **Erfan Ghadirzadeh:** Project administration; supervision; validation; visualization; writing – review and editing. **Elham Charkazi:** Data curation; resources; software. **Parastoo Ghorbani:** Formal analysis; writing – review and editing.

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None.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data are available with the corresponding author and can be reached on request.

ETHICS APPROVAL STATEMENT

Not applicable.

CONSENT

The authors declare that appropriate written informed consent was obtained from the patient and her legal guardian for publication of this case report.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

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