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Low molecular weight heparin induced late onset thrombocytopenia leading to post-partum hemorrhage: A rare case report

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Abstract
Background: Heparin induced thrombocytopenia (HIT) is an immune mediated adverse reaction to heparin characterized by thrombocytopenia and paradoxical prothrombotic state. Late onset HIT, occurring after heparin discontinuation, is a recognized but uncommon entity that poses significant diagnostic and therapeutic challenge, particularly in obstetric patients.
Case description: A 36-year-old female, Gravida 3 Abortion 2, with trichorionic triamniotic triplet pregnancy conceived through *in vitro* fertilization (IVF) with one fetal reduction done at 3 months of amenorrhea with cervical cerclage. She was commenced on therapeutic heparin for thromboprophylaxis. At 36 weeks of gestation, cesarean section was planned for fetal compromise. Heparin was discontinued 24 hours before the surgery. Postoperatively inspite of uterus being well contracted, she developed vaginal bleeding and hematuria which raised suspicion of late onset HIT. The bleeding did not respond to regular antifibrinolytics and quickly responded to protamine sulphate which made us think it to be late onset HIT.
Conclusion: Late onset heparin induced thrombocytopenia is rare but life-threatening complication that may develop after heparin cessation and outside the classic 5-to-10-day window. A high index of index of clinical suspicion, thorough heparin exposure history, and prompt multidisciplinary management are essential to optimize maternal outcome.

Keywords: Heparin induced thrombocytopenia, Post-partum hemorrhage, Protamine sulphate, Thrombocytopenia, Obstetric anticoagulation

Introduction

Heparin-induced thrombocytopenia (HIT) is a well-recognized immune-medicated complication of heparin therapy, occurring in approximately 0.5-5% of patients receiving unfractionated heparin therapy and less commonly with low molecular weight heparin (LMWH). The condition is characterized by a paradoxical hypercoagulable state arising from platelet activation medicated by IgG antibodies directed against complexes of platelet factor 4 (PF4) and heparin. The resultant thrombocytopenia, combined with a prothrombotic milieu, can precipitate life-threatening arterial and venous thrombosis, as well as consumptive coagulopathy leading to disseminated intravascular coagulation (DIC) [1, 2].

The classical presentation of HIT manifests between 5 to 10 days following initiation of heparin therapy. However, a delayed variant - late onset or "delayed" HIT has been increasingly recognized in literature. In this variant, thrombocytopenia and thrombotic complications may appear 5 to 19 days or more after heparin has been discontinues, posing a significant diagnostic challenge to clinicians who may not connect the clinical presentation to prior heparin exposure [3, 4].

In the obstetric setting, heparin represents the cornerstone of thromboprophylaxis and treatment of thromboembolic disease, given its established safety profile regarding placental transfer. The occurrence of late onset HIT associated with DIC in a high-risk obstetric patient therefore carries dual implications - both hemorrhage and thrombotic risks to the mother, compounded by placental compromise and fetal jeopardy. To the best of our knowledge, late onset heparin induced thrombocytopenia following caesarean delivery (30 hours after cessation of heparin) represents a rare clinical scenario.

We herein report such a case managed at our institution, highlighting the pathophysiological mechanisms, diagnostic considerations, and the multidisciplinary approach required to achieve favorable maternal outcome.

Case Report

A 36-year-old female, G3A2, presented to our department with a trichorionic triamniotic triplet pregnancy conceived via *in vitro* fertilization (IVF) with fetal reduction which was performed approximately 3 months of amenorrhea, resulting in dichorionic diamniotic twin pregnancy with cervical stitch placed in situ. In view of the inherent thromboembolic risk associated with assisted reproductive technology, multiple gestation, and her obstetric history, she was initiated on heparin thromboprophylaxis early in pregnancy.

The antenatal course was otherwise uneventful until a growth scan at 36 weeks revealed severe oligohydramnios in Fetus A and mild oligohydramnios in Fetus B, indicative of uteroplacental insufficiency. Given the evidence of fetal compromise, a lower segment caesarean section (LSCS) was planned. Heparin was discontinued 24 hours prior to the procedure in accordance with standard obstetric anticoagulation protocols.

The caesarean section was performed without intraoperative complication and two live babies were delivered. However, in the immediate postoperative period uterus was well contracted thus ruling out atonic PPH and there were no other causes of traumatic PPH as well. The patient developed primary postpartum hemorrhage per vaginum and gross hematuria, raising clinical suspicion of coagulopathy. Active uterotonic management was instituted with oxytocin, carboprost, and misoprostol.

Laboratory investigations confirmed a consumptive coagulation consistent with DIC: thrombocytopenia (platelet count - 90,860/mm^3), elevated D-Dimer (1.8 µg/mL), INR (1.1), prolonged prothrombin time (PT - 22 seconds) and activated partial thromboplastin time (aPTT - 52 seconds). A careful review of the patient's history, noting recent heparin exposure discontinued within the preceding 24 hours, raised the clinical suspicion of late onset HIT.

Protamine sulphate, the specific heparin antagonist, was administered intravenously at an appropriate dose to neutralize residual heparin activity. Following protamine administration, hematuria resolved progressively, coagulation parameters began to normalize quickly, and the postpartum hemorrhage was controlled. The patient was monitored closely in the intensive care unit before being stepped down to the post-natal ward. The mother made a full clinical recovery.

Discussion

HIT is classified into two types. Type I HIT is a non-immune, transient, and clinically benign form of mild thrombocytopenia that resolves despite continuation of heparin. Type II HIT, which is clinically significant form, is immune-mediated and characterized by the generation of IgG antibodies against PF4-heparin complexes. These antibodies activate platelets via FcγRIIA receptors, leading to platelet consumption, thrombocytopenia, and paradoxical hypercoagulability culminating in thrombus formation and, in severe cases, DIC [2].

Classically, the platelet nadir in Type II HIT is observed between days 5 and 10 after heparin initiation - the time required for IgG antibody production. However, "delayed" or late-onset HIT is a recognised entity in which the syndrome manifests or persists after heparin has been discontinued. Rice *et al*. (2002) described cases of delayed-onset HIT occurring up to 19 days after heparin cessation, attributing this phenomenon to two principal mechanisms. First, high-titre anti-PF4/heparin antibodies may persist in the circulation and continue to activate platelets in the presence of endogenous heparinoids such as glycosaminoglycans on the endothelial cell surface. Second, the antibodies may recognise PF4 bound to endothelial glycosaminoglycans even in the complete absence of exogenous heparin, sustaining platelet activation and procoagulant activity beyond the period of heparin exposure [3, 4].

The recognition of late-onset HIT is particularly challenging because clinicians may not attribute new-onset thrombocytopenia or coagulopathy to heparin once the drug has been discontinued. This underscores the critical importance of obtaining a thorough and systematic history of all prior heparin exposures - including the route, formulation, and duration - in any patient presenting with unexplained thrombocytopenia, thrombosis, or DIC in the postoperative or postpartum period. The diagnosis should prompt immediate cessation of all heparin products and avoidance of platelet transfusions unless the patient has life-threatening haemorrhage, as transfusions may paradoxically fuel further thrombosis [4, 6].

In the present case, the diagnosis of late-onset HIT was established on clinical grounds given the temporal relationship between heparin discontinuation and the onset of haemorrhagic complications, supported by laboratory evidence of consumptive coagulopathy. The decision to administer protamine sulphate was guided by the need to neutralise residual circulating heparin in the acute haemorrhagic setting, and the clinical response confirmed residual heparin as a contributing factor [5].

It is noteworthy that obstetricians are traditionally less accustomed to the use of protamine sulphate, as its administration is more commonly encountered in cardiac surgery and critical care settings. However, with the increasing use of low molecular weight heparin (LMWH) in obstetric practice for thromboprophylaxis and treatment of thromboembolic disorders, there is a growing need for obstetricians to be familiar with the indications, dosing, and safe administration of protamine sulphate [7, 8, 9].

Protamine sulphate, while effective, is not without potential adverse effects. These include hypotension due to rapid intravenous administration, bradycardia, pulmonary hypertension, and, in rare cases, catastrophic anaphylactic reactions [10, 11]. Protamine sulphate is generally available in tertiary care centres and major hospitals, though accessibility may be limited in peripheral or resource constrained settings. It is marketed under various pharmaceutical brands and is typically supplies in injectable form (commonly 10 mg/mL). The approximate cost ranges from 50 to 150 rupees per ampoule, making it relatively affordable, particularly in emergency obstetric care settings.

The obstetric context adds additional layers of complexity. In pregnancy, both thrombotic and haemorrhagic complications of HIT carry dual risk to mother and fetus. Placental thrombosis may cause intrauterine growth restriction, oligohydramnios and preterm delivery - features observed in this case. The postpartum haemorrhage superimposed on HIT substantially elevated the risk of hypovolemic shock and end-organ damage. The multidisciplinary involvement of obstetrics, haematology, and neonatology was therefore essential, as was the early recognition of the syndrome and targeted pharmacological reversal [12, 13].

Conclusion

Late-onset heparin induced thrombocytopenia is a rare but

potentially catastrophic complication that must be considered in any obstetric patient developing unexplained coagulopathy or thrombocytopenia in the operative or postpartum period, particularly in the context of recent heparin exposure. The condition may arise beyond the classical 5-10-day window, even after heparin has been discontinued, due to the persistence of high-titre anti-PF4 antibodies and their interaction with endogenous endothelial heparinoids.

In the setting of a high-risk multiple IVF pregnancy, where heparin thromboprophylaxis is standard of care, awareness of this rare complication is imperative. A systematic heparin exposure history, a high index of clinical suspicion, and prompt institution of targeted therapy - including heparin reversal with protamine sulphate in the acute haemorrhagic setting and substitution with alternative anticoagulation - alongside a coordinated multidisciplinary approach, are the cornerstones of successful management. Timely recognition and intervention can be life-saving for both the mother and the neonate.

Declarations

Patient consent: Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest: The authors declare no conflicts of interest.

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