

Heparin-induced thrombocytopenia occurring in the first trimester of pregnancy: successful treatment with lepirudin. A case report

The management of heparin-induced thrombocytopenia (HIT) in pregnancy represents a medical challenge. The advent of new antithrombotic agents that do not cross-react with platelet factor 4 and heparin antibodies represents an important progress, and they are of utmost interest in special situations such as early pregnancy, a situation where the teratogenicity of warfarin precludes its use.

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The direct thrombin inhibitor lepirudin has been demonstrated to be safe and effective for the prophylaxis as well as for the treatment of venous thromboembolism.¹ However, the exact role of these new compounds in the therapeutic approach of pregnant women with HIT has not been well defined yet.

The present case report describes the clinical course and management of a 10-week pregnant woman with cerebral venous thrombosis who was successfully treated with lepirudin for HIT, and was then reexposed to heparin in the peripartum with no immune response rebound.

A 27 year-old female at 8 weeks gestation was hospitalised because of hyperemesis and persistent headache. On day 3 she became stuporous, and was diagnosed with a cerebral venous thrombosis involving superior sagittal, rectus and right transverse sinus by cerebral CT scan. She was transferred to an intensive care unit, and was treated with intravenous unfractionated heparin (UFH). One week later, her clinical condition improved, and she was switched to low molecular weight heparin (LMWH), enoxaparin at 6000 units twice daily. While on LMWH, she had a syncopal episode associated with hypotension, tachycardia and profuse sweating. A diagnosis of pulmonary embolism was made, based on the echocardiogram finding of a severe right ventricular dilatation associated with pulmonary hypertension. Intravenous heparin was started over, and the patient was transferred to our institute, where UFH treatment was continued. Nine days later (on day 16 from the first heparin exposure) the platelet count dropped to $111 \times 10^9/L$, more than 50% reduction from baseline ($307 \times 10^9/L$). Her platelet factor 4-heparin enzyme immunoassay (performed by the PF4 enhanced assay from GTI diagnostics, Waukesha, WI, USA) was positive (OD = 1.08, cut-off > 0.4). Neither clinical manifestations of new thrombotic events nor evidence of cerebral venous thrombosis progression were present. Heparin therapy was immediately discontinued, and the patient was started on intravenous r-hirudin, lepirudin, at 0.15 mg/kg/h. After one week her platelet count had recovered, and she was converted to subcutaneous lepirudin at 1 mg/kg every 8 h to achieve a therapeutic aPTT (from 1.5 to 2.5 times the normal value). The patient was discharged on subcutaneous lepirudin, and then switched to warfarin at her 14th week of pregnancy. No platelet factor 4-heparin antibodies were found by ELISA at the 32nd week of pregnancy.

Oral anticoagulation was stopped three days before the scheduled caesarean, and this allowed to reach a normal INR on the day of delivery (at the 36th week of gestation). The patient successfully underwent an uncomplicated caesarean delivery. The physical examination of the new-

born was normal; her neonatal weight was 2660 g (50th centile), length 47.5 cm (50th centile) and head circumference 32.5 cm (50th centile). The mother was then started on nadroparin 6000 units twice daily and warfarin on the same day of delivery. Nadroparin was discontinued after 4 days from delivery when a therapeutic INR was reached. Both mother and child were sent home in healthy condition.

Pregnancy has been found to be associated with a 4-times higher risk of venous thromboembolism.² Among venous districts, cerebral veins and sinuses represent a common site of pregnancy or puerperium-associated thrombosis.³ Pulmonary embolism occurs in about 10% of cases, and it is associated with 95% mortality. Heparin has been widely accepted as first line therapy in cerebral vein thrombosis, and it should be followed by oral anticoagulation therapy.⁴ In pregnant women, warfarin can be safely administered starting from the second trimester. Our case is of particular interest, as an empirical approach was taken to successfully treat cerebral vein thrombosis and pulmonary embolism complicated by HIT in a pregnant woman during the first trimester.

Mehta et al.⁵ have already described a case of HIT at 7 weeks gestation managed with lepirudin. In that case, lepirudin administered s.c. up to 125 mg twice a day was associated with an initial recrudescence of thrombosis-related symptoms. As lepirudin has a plasma half-life of approximately 60 min after intravenous injection, and approximately 120 min after subcutaneous injection,⁶ a twice-daily schedule of administration will probably fail to reach a stable therapeutic range. In our case we found that lepirudin administration of 1 mg/kg three times a day was successful in reaching an aPTT level ranging between 1.5 and 2.5 the control value throughout the whole course of treatment, and no signs and symptoms indicative of disease progression nor significant side effects were noted.

There is evidence that reexposure to heparin does not necessarily trigger antibodies in patients with a distant history of HIT and no detectable antibodies at the time of reexposure.⁸ It has been proposed that, in this group of patients and in particular when HIT precedes reexposure of more than 6 months, short-term reexposure to heparin (<5 days) may be safe.⁸ The presence of HIT antibodies by ELISA must be ruled out before considering short-term heparin reexposure. For these reasons, our therapeutic option in the peripartum period was to administer nadroparin for less than 5 days, as a bridge to warfarin after birth. A four-day period of reexposure to LMWH did not affect platelet count, and no HIT-associated antibodies were detected by ELISA after delivery.

This case report further supports the rationale to consider subcutaneous lepirudin in a relatively long-term therapy of pregnant outpatients with HIT. As previously reported, prenatal exposure to lepirudin did not adversely affect the developing fetus.^{5,9-11} In spite of the very low number of exposed fetuses, the lack of evidence of teratogenic effects makes this drug a valid option in pregnancy when heparin cannot be used. Furthermore, it also adds more evidence in favour of short-term heparin reexposure in patients with a history of HIT but no detectable antibodies. However, a word of caution must be spent as it is not known whether direct thrombin inhibitors cross the placenta, and thus their potential embryotoxic or teratogenic effects cannot be completely excluded.

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