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Case report 2

Prothrombin deficiency: a rare bleeding disorder complicated with a large retroplacental haematoma

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Key words: prothrombin pregnancy, antepartum haemorrhage, pregnancy loss

Abstract

Inherited factor II deficiency is a rare bleeding disorder which is caused by variations in factor II gene. Limited data is published on bleeding risk and management of these patients during pregnancy. According to available data antepartum haemorrhage (APH), postpartum haemorrhage (PPH) and pregnancy loss are common complications in pregnant females with factor II deficiency. This 26 year old woman with prolonged PT and APTT was in her first pregnancy. She had a history of spontaneous mucocutaneous bleeding and menorrhagia. Her factor II level done at 12 weeks of gestation was 3.7%. She was started on prothrombin complex concentrate (PCC) 1000 IU once per week after confirmation of the diagnosis. Despite PCC prophylaxis she developed a large retroplacental haematoma and ended up in a second trimester miscarriage. This was managed with increased doses of PCC, red cell transfusions and tranexamic acid infusions. Management of pregnancy in factor II deficiency requires a multi disciplinary approach. In resource poor settings outcome of pregnancies is affected by limitations of laboratory facilities for factor level monitoring and lack of psychosocial support.

Introduction

Prothrombin (Factor II) deficiency can be either acquired or congenital. Congenital prothrombin (F2) deficiency is an autosomal recessive disorder in which reduced plasma prothrombin activity is caused by quantitative (hypoprothrombinaemia) or qualitative (dysprothrombinaemia) defects in the factor II protein[1]. Inherited factor II deficiency is a rare bleeding disorder, and it has an estimated prevalence of 1 in 2,000,000[2]. Acquired factor II deficiency may occur in lupus anticoagulant hypoprothrombinaemia syndrome which can be distinguished from congenital factor II deficiency on clinical grounds, PT and APTT mixing studies and the presence of antiphospholipid antibodies[3]. Factor II is required in the common pathway of the coagulation cascade. It is activated to the serine protease, thrombin by activated factor X in the initiation phase of coagulation and by the prothrombinase complex in the amplification phase. Factor II deficiency is caused by variations in the factor II gene and there is a poor association between factor II genotype and clinical phenotype[4]. Limited data is published on bleeding risk and management of these patients during pregnancy.

Case report

This 26-year-old woman was first referred to haematology clinic in 2018 at the age of 20 years due to prolonged Prothrombin Time (PT) and prolonged Activated Partial Thromboplastin Time (APTT). She was born to non-consanguineous parents of Muslim origin from Muththur area in Trincomalee district, Sri Lanka. Her birth history was uneventful, and she had three elder siblings who were apparently healthy without any history of bleeding diathesis. During childhood she suffered from easy bruising and then menorrhagia since her menarche. She was treated with haematinics

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several times and not further investigated. There was neither history of excessive bleeding from cut injuries or wounds nor any family history of bleeding disorders. There was no history of any blood or component transfusions during childhood. At the age of 12 years, she was diagnosed with an intestinal obstruction, and underwent an exploratory laparotomy. There were no records of coagulation studies performed at that time. She was not aware of any excessive blood loss; however, she could remember that she received one or two blood transfusions post operatively.

In 2018, she was diagnosed with spinal tuberculosis. The coagulation profile performed during this time revealed prolonged PT and APTT values of 38 seconds 53 seconds respectively. The 50:50 mixing studies for both PT and APTT values showed correction of PT and APTT with values of 15 seconds and 32 seconds respectively. A factor deficiency (Factor II, V, combined factor V and VIII or Factor X) was suspected and factor assays were arranged. However, she defaulted and did not attend the routine haematology clinic follow up. Two years later in 2020 she was again referred by the Obstetric team with a period of amenorrhoea of 10 weeks and a positive pregnancy test. There were no bleeding manifestations.

Her full blood count showed haemoglobin of 12.4 g/dL with normal red cell indices, normal white cell counts and a normal platelet count. The blood picture findings were within normal limits and the renal and liver function tests were normal.

The coagulation profile and mixing studies performed at 12 weeks of gestation are tabulated in Table 1.

The inhibitor screen was negative. Since both the APTT and PT were corrected with pooled normal plasma, she was referred to National Hospital of Sri Lanka for further factor assays. Her factor II levels were reported as 3.7% (50-150%). Factor V and X levels were not available at that time hence it was not performed. The diagnosis was tentatively confirmed as factor II deficiency.

Her antenatal scan revealed a single live fetus and there were no haemorrhages. To exclude the rare possibility of antiphospholipid syndrome, anti cardiolipin antibodies and anti beta 2 glycoprotein 1 antibodies were performed. DRVVT was planned to be performed after the delivery.

A multi disciplinary team (MDT) discussion involving haematology, obstetric and the paediatric teams was held regarding the management of her pregnancy. She was started on PCC prophylaxis at a dose of 1000 IU once per week. She was advised to avoid strenuous exercise, non steroidal anti inflammatory drugs and intramuscular injections. She was provided with stockings and advised on adequate oral hydration as preventive measures of thrombosis.

While on PCC prophylaxis at 15 weeks of the pregnancy she presented with mild abdominal pain and the ultrasound scan revealed a retroplacental haematoma of 10 cm × 15 cm in size.

Table 1. Results of coagulation studies at diagnosis

Description	PT (seconds)	APPT (seconds)	TT (seconds)	Clauss Fibrinogen
_	67.8 (9.5 - 13.5)	60.6 (26 - 35)	14.3 (11 - 18)	210 mg/dl (150 - 350)
50:50 mix with pooled normal plasma	12.1	26	_	_

She was admitted to the obstetric ward and blood samples were sent for urgent full blood count, coagulation profile, renal functions, liver functions and group and save. She was started on IV Tranexamic acid. The vital parameters were monitored closely. The PT and APTT values were fluctuating in normal to marginally elevated range. There were no facilities to monitor factor II levels closely. As the haematoma gradually increased in size within a week the PCC prophylaxis dose increased to 1000 IU two times per week. Despite repeated explanations she refused to stay in the ward and there were no facilities to keep a stock of PCC at her home as well. Compliance became an issue as she was not attending on the given dates.

The haematoma expanded and she ended up with a miscarriage at 20 weeks of gestation. This was successfully managed with PCC, tranexamic acid and red cell transfusions. She was discharged home without any further complications and the contraceptive advice was provided by the obstetric team. DRVVT performed later was negative for antiphospholipid antibodies. Currently she is being followed up at haematology clinic with clinical monitoring for bleeding and routine full blood counts. Factor V, X and VIII levels were planned but could not be performed yet due to practical issues.

Discussion

Prothrombin is a 72 KDa vitamin K dependent glycoprotein which has plasma concentration of approximately 100 micg/mL[5]. Prothrombin deficiency can be inherited or acquired. The acquired prothrombin deficiency occurs in patients with vitamin K deficiency, liver disease, patients on warfarin or in the presence of inhibitors in patients with lupus anticoagulant hypoprothrombinaemia syndrome[6]. The inherited factor II deficiency is the rarest coagulation factor disorder[7].

In this patient there was no evidence to suggest an aquired cause and the condition is most likely to be inherited since she gave a history of a bleeding tendency since childhood. In cases of Iranian and Indian registries, the most common symptoms were mucocutaneous, soft tissue, joint, surgical and heavy menstrual bleeding[1]. In this young lady mucocutaneous bleeding and menorrhagia were the predominant bleeding manifestations.

Bleeding caused by factor II deficiency was more severe in cases with factor II activity <0.1 iu/mL than in those with factor II activity >0.1 iu/mL, who typically experience mild mucocutaneous bleeding[7]. In this patient the factor level was 3.7% which explains the bleeding phenotype. In a case report, life threatening menorrhagia was present in a 22 year old woman and the coagulation work up identified her to have deficient factor II activity[8]. However in our patient menorrhagia was not further investigated and she remained undiagnosed until adulthood. At the time of the surgery also her bleeding risk might have not been properly assessed and no coagulation studies were done. As per the BCSH recommendations further coagulation studies are indicated in patients with risk of bleeding based on the clinical history[9].

Women with inherited bleeding disorders are particularly at risk of bleeding complications during pregnancy. They require specialised and individualised care. The general principles of the management of pregnancy, delivery and the postpartum period in patients with rare bleeding disorders are the same. Limited data is published on bleeding risk and management of factor II deficiency in pregnancy.

Factor II levels do not increase during pregnancy[10]. Case reports have described associations among factor II deficiency and APH, pregnancy loss and PPH. APH, PPH and pregnancy loss were identified in two case series of 22 pregnancies in women with factor II deficiency[1]. The BCSH guidelines suggest to consider long term prophylaxis for cases with personal or family history of severe bleeding or with factor II activity <0.01 iu/mL, using PCC 20-40 iu/kg once week, adjusted to maintain trough factor II activity >0.1 iu/mL. The RCOG guidelines also suggest that PCC prophylaxis can be continued in pregnant females with factor II deficiency. In our patient there was no personal or family history of severe bleeding and her factor levels were around 3%. Considering the limited information on management of such pregnancies and the lack of

facilities for monitoring, the MDT decision was to start her on prophylaxis. She was started at a dose of 20 iu/kg once per week. The facilities for monitoring factor levels were not freely available. Despite increasing the prophylactic PCC dose she developed a large retroplacental haematoma and unfortunately the pregnancy ended up in a miscarriage in the second trimester. We were able to manage the delivery of retained products of conception with blood product support, IV tranexamic acid and PCC according to standard recommendations. The differential diagnosis for prolonged PT and APTT includes factor V, factor X and combined factor V and VIII deficiency as well. Even though the factor II levels were low the aforementioned deficiencies are also possible. So, these factor levels should also be performed for a confirmatory diagnosis and future management of this young woman.

Ideally pregnant patients with rare bleeding disorders should be managed in tertiary care obstetric units with facilities to manage potential bleeding episodes and close monitoring of factor levels. Management of these patients are challenging in resource poor settings. Limitations such as unavailability of adequate laboratory facilities and psychosocial support for patients affect the outcome of the pregnancy.

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