Antenatal identification of factor VII Padua during a healthy pregnancy: implications for labor and delivery

Abstract: We present a case in which a 28-year-old pregnant woman (para 1) was suspected to have inherited factor VII (FVII) deficiency following investigation for recurrent mild easy bruising. However, this was ruled out by identification of a rare FVII variant not associated with an increased bleeding risk. This allowed usual obstetric care to proceed without any restrictions, facilitating an uncomplicated spontaneous vaginal delivery at term.

Keywords: factor VII Padua; pregnancy.

Introduction

It is critical that pregnant women with inherited bleeding disorders are appropriately managed at the time of labor and delivery to minimize the risk of bleeding complications in the mother and in the potentially affected fetus [6]. Care pathways are jointly agreed upon by a multidisciplinary team experienced in the management of these disorders in pregnancy. These care pathways advise on interventions associated with maternal and fetal bleeding risk, including regional anesthesia and instrumental delivery. While these recommendations are generally successful in preventing bleeding, they may pose significant challenges to normal obstetric care. We present a case in which a suspected inherited factor VII (FVII) deficiency in a pregnant woman was ruled out by identification of a rare FVII variant not associated with an increased bleeding risk, allowing usual obstetric care to proceed without any restrictions.

Case report

A 28-year-old Nigerian woman was referred by her obstetric team to the hematology service, Rotunda Maternity Hospital, at 13 weeks of gestation in her second pregnancy. The referral was made as she reported having been diagnosed with FVII deficiency. Her diagnosis of FVII deficiency had come to light prior to her current pregnancy at a separate institution during investigation of mild easy bruising. She had no family history suggestive of any underlying bleeding disorder. No additional bleeding history was reported. Her first pregnancy had been uncomplicated, and she had delivered vaginally at term.

Activated partial thromboplastin time (APTT), fibrinogen, and full blood count were normal; however, a prothrombin time (PT) was prolonged at 32 (12–15) s. Plasma FVII activity was measured in a one-stage PT-based assay using rabbit brain thromboplastin, which indicated reduced plasma FVII activity at 0.04 (0.60–1.40) IU/mL. The patient, now pregnant, was referred to the Irish National Centre for Hereditary Coagulation Disorders (NCHCD), where a repeat plasma FVII assay, also utilizing rabbit brain thromboplastin, confirmed a reduced plasma FVII level, at 0.07 (0.51–1.54) IU/mL. Her partner’s FVII level was normal. Interestingly, it was noted that the patient’s PT was now within normal limits, at 11.8 (9.6–12.3) s and 11.0 (10.5–13) s in assays performed in the Rotunda Hospital and the NCHCD, respectively.

In line with consensus guidelines [1, 4, 6], an initial labor and delivery plan was provisionally agreed upon pending further investigations, with the aim of preventing maternal and fetal bleeding complications in the setting of an apparently subhemostatic plasma FVII level. Specific recommendations were made to avoid regional anesthesia, instrumental delivery, the use of fetal scalp sampling and electrodes, and intramuscular injections.

Subsequent investigations aimed to resolve the unusual discrepancy between results of PT assays performed in the various institutions involved in the patient’s...
care. A careful review of assay methods used in each hospital laboratory revealed that recombinant human thromboplastin was used as a source of tissue factor in the Rotunda Maternity Hospital and in the NCHCD. In contrast, rabbit brain thromboplastin was used in the PT assay performed in the hospital where the patient was first investigated for easy bruising. It was hypothesized that the patient might have a diagnosis of FVII Padua, a condition characterized by a discrepancy in FVII activity level depending upon the source of thromboplastin used in the assay but which is of no clinical significance and is not associated with an increased risk of bleeding [3].

To investigate this hypothesis, a FVII activity assay was repeated, substituting rabbit brain thromboplastin for recombinant human thromboplastin. Factor VII activity was normal in this assay, confirming a diagnosis of FVII Padua. All restrictions, which had provisionally been put in place to guide the management of labor and delivery, were removed. She went on to have a normal vaginal delivery, with an estimated blood loss of 300 mL. Regional anesthesia was not required.

**Discussion**

Upon vascular injury, coagulation is initiated when tissue factor (TF) on the surface of extravascular cells of the subendothelial matrix is exposed to blood [7]. Activated FVII (FVIIa) is a procoagulant clotting factor, which, upon binding to this exposed TF, plays a key role in the “extrinsic phase” of blood coagulation [7]. Prothrombin-based clotting assays measure the time taken for plasma to clot following the addition of a reagent containing TF (thromboplastin) and calcium [8].

True congenital FVII deficiency is the most common of the rare congenital bleeding disorders, with symptomatic inherited FVII deficiency occurring in 1 per 500,000 individuals [5]. More than 130 causative mutations have been identified, mostly point mutations frequently occurring in the largest exon of the factor 7 gene, exon 8. Factor VII deficiency is inherited in an autosomal recessive manner [1]. Clinical bleeding phenotype is variable, but symptoms can occur during the first 6 months of life in the most severe cases [5]. A point mutation (Arg304Gln) in exon 8 of the factor 7 gene gives rise to FVII Padua, a variant characterized by discrepancy in measured FVII activity in a one-stage PT-based FVII assay depending upon the source of thromboplastin used in that assay [3]. The FVII Padua mutation is located in close proximity to the tissue factor binding site on FVII. Marked reductions in FVII activity are observed in assays utilizing rabbit brain thromboplastin (4–10% of normal), while FVII activity is normal if ox-brain thromboplastin is used [2]. Recombinant human thromboplastin or human placental thromboplastin frequently results in intermediate FVII activity (30–40% normal) [2]. While plasma PT may be prolonged, again, this is dependent upon the source of thromboplastin used in the assay, neither this, nor the variable assay-dependent FVII activity translate into an elevated bleeding risk. Affected individuals may remain undiagnosed, a situation which is of no clinical consequence.

It is critical, however, that patients whose true phenotype is FVII Padua are not labeled with an erroneous diagnosis of inherited FVII deficiency, a condition which is associated with an increased bleeding risk [5]. Here, we report a case in which a correct diagnosis of FVII Padua was made in a pregnant woman with little significant bleeding history.

Restrictions imposed upon obstetric management of labor and delivery in women with true bleeding disorders including hemophilia and rare coagulation disorders are appropriate and essential to prevent maternal and fetal bleeding complications. However, these restrictions are not imposed lightly, and are not without potential complications. A recommendation to avoid regional anesthesia may translate into significant pain and psychological distress during prolonged labor where epidural anesthesia is precluded and may expose a woman requiring a cesarean section to the risks associated with general anesthesia where spinal anesthesia is contraindicated. Moreover, a restriction on forceps and vacuum delivery may necessitate conversion to an emergency cesarean section in a mother undergoing a difficult labor with suboptimal progress. Removing these restrictions where appropriate and communicating this change of management clearly to obstetric colleagues is critical.

In conclusion, we report a case in which multicenter, multidisciplinary investigation and management of a pregnant woman with a prolonged clotting time facilitated timely provision of a correct diagnosis, thus, avoiding exposure to the potential restrictions mandated with bleeding disorders in labor and delivery.

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