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A Pandora's box of postpartum hemorrhage in pregnancy

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Abstract
Inherited combined factor V and factor VIII deficiency (F5F8D) is autosomal recessive transmission disorder. Epistaxis, postsurgical bleeding, and menorrhagia are the most common symptoms. Other types of bleeding can occur, including hemarthrosis and muscular hematomas [1]. Mutations in two genes- lectin mannose binding protein 1 (LMAN1) and multiple coagulation factor deficiency (MCFD2) is the cause of F5F8D [2]. We report here a 27yr old patient born of third consanguineous marriage second gravida with previous miscarriage was admitted in early labour of a spontaneous pregnancy at 38 weeks. Following increased bleeding during dilation and curettage of previous miscarriage, patient was evaluated and diagnosed to have F5F8D. Parturient was admitted in intensive care unit, maternal and fetal monitoring was performed. Fresh frozen plasma concentrates were perfused during labor. Patient had traumatic PPH due to vaginal laceration which was repaired. Patient reported with secondary PPH two weeks later for which obstetric hysterectomy had to be resorted. Patient was monitored with daily factor V and VIII level and accordingly FFP and factor VIII was administered till wound healing. Surprisingly HPE reports of uterus showed cavernous hemangioma of endometrium. The symptomatology is not unequivocal and when it occurs during pregnancy or postpartum, it causes life-threatening cataclysmic hemorrhage. Antenatal diagnosis is difficult and requires a multidisciplinary approach. The diagnosis is histological. The cavernous hemangioma is a rare benign vascular tumor. About 50 cases of this disease were found in the literature over the last century and only 9 cases of cavernous hemangioma on the pregnant uterus were published it comes into cavernous or capillary form [3].

Keywords: Pandora's box, postpartum hemorrhage, pregnancy

Introduction
Mutations in two genes- lectin mannose binding protein 1 (LMAN1) and multiple coagulation factor deficiency (MCFD2) is the cause of F5F8D [2]. Inherited combined factor V and factor VIII deficiency (F5F8D) is autosomal recessive transmission disorder, Oeri first reported it in 1954 [2]. Studies of the inheritance pattern indicated that it was likely to be due to a single gene defect rather than due to coinheritance of separate defects of the FV and FVIII genes. This has been confirmed, the gene being located on the long arm of chromosome 18. The gene encodes a resident protein of the endoplasmic reticulum, the golgi intermediate compartment, termed the ERGIC-53 protein [5-10]. This protein has been identified as playing a major role in intracellular trafficking of certain proteins including FV and FVIII. Although it would appear that within hepatocytes FV and FVIII are synthesized normally, defective ERGIC-53 function results in disturbance of the passage of the factors through the cell and impaired release into the circulation. A number of different mutations have been described in this gene leading to combined FV and FVIII deficiency [9, 10]. Combined FV and FVIII deficiency is a serious problem in obstetrics, because during the pregnancy and postpartum carry a high bleeding risk [1]. There is little literature available on this subject and there are no guidelines available concerning management in pregnancy. Incidence of combined F5F8D is one per one million [11]. Epistaxis, postsurgical bleeding, and menorrhagia are the most common symptoms. Other types of bleeding can occur, including hemarthrosis and muscular hematomas. There is increased risk of miscarriage and placental abruption resulting in foetal loss or premature delivery in women with bleeding disorders [12, 13]. Patients with this disorder usually have mild to moderate bleeding symptoms and concomitantly low levels of FV and FVIII between 5% and 20%. The combined deficiency disorder is associated with a prolongation of both the PT and APTT, with the APTT prolongation disproportionate to that of the PT.

Both test times are corrected by mixing studies using normal plasma. APTT-based activity assays and antigen assays reveal levels of between 5 and 20 IU dL)1 for both FV and FVIII [14]. FV levels in pregnancy do not consistently increase or decrease whereas FVIII levels will increase throughout pregnancy: any possible bleeding is therefore likely to be dependent on the FV level during labour and postdelivery. The cavernous hemangioma is a rare benign vascular tumor. About 50 cases of this disease were found in the literature over the last century and only 9 cases of cavernous hemangioma on the pregnant uterus were published it comes into cavernous or capillary form [3].

Case report

27yr old born of third consanguineous marriage second gravida with previous miscarriage was admitted in early labour of a spontaneous pregnancy at 38 weeks. Following increased bleeding during dilation and curettage of previous miscarriage, patient was evaluated and diagnosed to have F5F8D. Her past history revealed concept of frequent bruising after fall. She did have complaints of menorrhagia or menstrual disturbances. Baseline laboratory investigations showed prolonged bleeding time of 3min 30seconds, prolonged aPTT of 64.4, PT mix 12.2, INR 1.04, platelet count of 2.03lakhs/cu.mm, decreased factor VIII level of 10.3(17%) and factor V level of 8 (7.4%). DRVT for lupus anticoagulant was negative. Ristocetin cofactor assay (vWF:RCo) was normal 149.2%. Fibrinogen was 466 mg/dl. Antenatal period was uneventful. At term patient was admitted for in early labour and labour was augmented with Injection oxytocin. On admission, the laboratory parameters were the same with factor VIII level of 17% and factor V level of 7.4%. Intrapartum fetal and maternal well being were monitored and patient received fresh frozen plasma transfusion during labour. During second stage patient had profuse bleeding and second stage labour and a healthy baby of weighing 3.05kg with good APGAR of 9/10 was delivered. Lateral vaginal wall tear was noted and same was repaired. Patient got discharged on post natal day 5. Two weeks later patient presented with secondary PPH with hypotension. Patient was resuscitated with 3 units packed cells, 12 units FFP and one unit cryoprecipitate. Bleeding was controlled with injection tranexamic acid. Three days later patient again had a heavy bout of bleeding which was not controlled with medical management and Bakri balloon tamponade. Emergency obstetric total abdominal hysterectomy with bilateral internal iliac artery ligation was done. Following which patient was monitored daily with factor V and factor VIII level assay and accordingly transfused with FFP and factor VIII for a week. Neonate had normal laboratory parameters. Histologically, endometrium focal area composed of large dilated and cavernous vascular spaces lined by flat and bland endothelial cells consistent with cavernous hemangioma of endometrium.

Discussion

In F5F8D, our knowledge about the clinical manifestation so far is based on just few large series published in the literature. Patients with this disorder usually have mild to moderate bleeding symptoms and concomitantly low levels of FV and FVIII between 5% and 20% [2, 4]. It was the case of our patient. The FV level is likely to be the main determinant of bleeding risk at delivery, because FVIII levels increase during pregnancy but FV levels remain the same. FV and FVIII levels should be checked during the third trimester so that a delivery plan can be made [3]. Our patient results remained unchanged before and during the pregnancy. The latter does not seem to worsen this deficiency. During labor, FFP at an initial dose of 15 to 20 mL/kg should be used to maintain FV levels at more than 15 IU/dL, and recombinant FVIII concentrate should be used to maintain FVIII levels at more than 50 IU/dL [1-5]. If Caesarean section is carried out, it would be prudent to continue FV replacement until wound healing has healed in women with FV levels of <15 U dL [8, 9, 10]. Epidurals can be performed if the woman has FV levels of >15 U dL and FVIII >50 IU dL. Our patients factor V and factor VIII levels were monitored and FFP was administered accordingly. But the patient developed secondary PPH probably due to additional pathology of cavernous hemangioma as aggravating factor. A cavernous hemangioma of the uterus may either occur as an isolated lesion of the uterus or may be associated with pelvic or extra-pelvic hemangiomatosis. There have been eight case reports that describe isolated involvement of the uterus in pregnant women and highlight the importance of uterine cavernous hemangioma as a rare but important cause of refractory uterine bleeding at the time of delivery [15-18].

Conclusion

Pregnancy and childbirth present a major challenge to women with inherited bleeding disorders. All women should be managed by a multidisciplinary team in a center where the expertise, laboratory support, and factor treatment required to provide care for these patients are available at all times to manage unexpected complications.

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