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ORIGINAL ARTICLE

Miscarriage and recurrent miscarriage in patients with congenital factor V deficiency: a report of six cases in Iran

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Abstract Miscarriage and recurrent miscarriage have not been reported in women with congenital factor V (FV) deficiency. Here we describe cases of both miscarriage and recurrent miscarriage in women with congenital FV deficiency (FVD). We investigated six women with FVD from the southeast of Iran who had experienced miscarriage and recurrent miscarriage. Consequent diagnosis was made by routine coagulation tests as well as FV activity and antigen assays. To evaluate the presence of an inhibitor, a mixing study via prothrombin time (PT) assay was performed. All patients were investigated, and found to be negative for antiphospholipid syndrome. Demographic data and clinical presentations were obtained by standard questionnaire. The factor assays determined that all six women were suffering from moderate FVD. One had experienced eight miscarriages, while the others experienced two (two patients), three, and four episodes. Only one patient had a single miscarriage. Three of the women experienced successful delivery without medical intervention. Miscarriage and recurrent miscarriage should be considered as possible presentations of FVD to prevent its life-threatening consequences.

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Keywords Factor V deficiency · Miscarriage · Recurrent miscarriage

Introduction

Women with inherited rare bleeding disorders (RBDs) can present clinical manifestations that vary from mild to severe bleeding tendency. In contrast with men, these patients have more difficulties because they experience more bleeding episodes in their lifetime due to menses and reproduction. Lack of control over such events may lead to bleeding episodes that affect daily activity and quality of life [1, 2]. In addition, pregnancy and delivery are critical times during the life of women with RBDs, as deficiencies may lead to miscarriage and severe bleeding complications. During pregnancy, the level of some coagulation factors, including Fibrinogen, factor VII, factor VIII (FVIII), are significantly increased while others including factor II, factor IX, factor X, and factor V (FV) do not significantly change [3, 4]. Although these result in a hypercoagulable state that, in patients with RBDs, may improve their haemostatic state; in some cases severe deficiency of coagulation factors leads to an increased risk of miscarriage [3, 4]. Due to the rarity of such life-threatening episodes in these patients, we did not find any cases of congenital FV deficiency (FVD) with miscarriage or recurrent miscarriage in our review of the literature. We found that some studies reported FVD patients who had a successful delivery following a specific prophylactic regime [5–7]. Sistan and Baluchestan Province, in the southeast of Iran, has a considerable number of patients with RBDs, of which 40 have FVD. Six experienced miscarriage or recurrent miscarriage as an unreported clinical manifestation. Therefore, this study aims to report demographic characteristics, clinical manifestations and obstetric histories of these patients.

Table 1 The demographic characteristics of patients with FV deficiency and a history of recurrent miscarriage

Patient	Age	Age at diagnosis	The factor V activity	Classification	Family history	Parental consanguinity	History of miscarriage (times)	Successful delivery (times)	Inhibitors	Other clinical features
1	37	36	3.5 %	Mod	+	+	8	–	–	DSH EP
2	21	20	5 %	Mod	+	+	3	1	–	GB EP
3	24	23	6.5 %	Mod	+	+	2	–	–	GB M EP
4	30	29	8 %	Mod	+	+	4	2	–	GB M EP
5	34	30	4.5 %	Mod	–	+	2	2	–	GB M EP
6	19	18	5.5 %	Mod	–	+	1	–	–	CB M EP

DSH deep soft tissue hematoma, *EP* epistaxis, *GB* gingival bleeding, *M* menorrhagia, *Mod* moderate

Patients and methods

This study was conducted on six patients with FVD that experienced miscarriage or recurrent miscarriage. All were selected from the haemophilia center in Zahedan in southeastern Iran. The study was approved by the medical ethics committee of Zahedan University of Medical Science. Initially, a hematologist examined the women. Their data were recorded by an expert staff and a physician in a standard questionnaire including demographic data (age, sex, and race), clinical manifestations and details of obstetric history, ethnicity, parental consanguinity, family history as well as kind of treatment, therapeutic response and complications of treatment. After clinical assessment, patients were referred to the coagulation laboratory of the Iranian Blood Transfusion Organization of Zahedan for routine screening tests. Bleeding time was determined via the Ivy method. Prothrombin time (PT), normal range 10–12 s, activated partial thromboplastin time (PTT), normal range 26–40 s, and thrombin time normal range 15–19 s, were assayed using standard instruments and techniques (Diagnostica Stago, kits and semi-automatic coagulation analyzer, STAGO, Start. France). To assay FV activity, the patients' plasma was mixed with commercial factor deficient plasma by PT-based assay, using an STA compact automatic coagulometer (Diagnostica Stago, France) [2]. In addition, FVIII activity was determined using the same method and instrument via PTT-based assay to differentiate FV deficiency from combined FV+FVIII deficiency. FV antigen assay was performed by the ELISA method (ELISA, Diagnostica Stago, France). All patients were evaluated for antiphospholipid syndrome as reported above [5]. Based on FV levels, patients were classified in three groups: severe deficiency with undetectable FV activity, moderate deficiency with <10 % of FV activity and mild deficiency with 10 % factor activity to normal range [8, 9].

Results

We report six women with FVD that presented with miscarriage or recurrent miscarriage as an extremely rare bleeding feature. The data of these patients are summarized in Table 1.

A total of 40 patients with congenital FVD were registered by the haemophilia center of Zahedan; among them 19 were female (47.5 %). Of these, eight (42.1 %) had a history of pregnancy with six (75 %) experiencing one or more miscarriages.

The other two women had no history thereof. The first was a 36-year-old woman with two successful deliveries; her FVD was diagnosed at 29. She was affected by moderate FVD (FV activity 1.4 %). She was the product of a consanguineous marriage and had a positive family history (one brother with FVD). The second was a 70-year-old woman with 10 successful deliveries; her FVD was diagnosed at 69 and her FV activity was 4.5 %. Their clinical manifestations were post-dental-extraction bleeding, purpura and deep soft tissue hematoma. All were negative for risk factors including antiphospholipid syndrome. Both PT and PTT tests were corrected by mixing the patients' plasma with normal plasma pool. No inhibitor against FV was detected in anyone.

Discussion

Sistan and Baluchestan Province, southeast Iran, has a high rate of RBDs (8–10). Its population of 2,700,000 includes 40 patients with FVD. Although this deficiency's features are usually mild, our patients' manifestations are moderate to severe with some unusual aspects first reported by our center in 2014 [5].

We described six women who presented with one or more miscarriages. Since FVD miscarriage is rarely reported, our literature review did not show any prior reference [4–6]. Almost 75 % of our patients with a history of pregnancy experienced recurrent miscarriage, which is a high frequency. Our previous study found that among sixteen women of the control population, only one (6 %) experienced a single miscarriage [9]. Since miscarriage is so rare, we assessed all six patients for antiphospholipid syndrome as well as genetic risks; no evidence of a secondary risk factor was observed. Therefore, we attribute these features to FVD with confidence. Three were sisters in a family whose other members, including two more sisters were unaffected by FVD or miscarriage. While recurrent miscarriage is not rare, it is a hallmark of factor XIII deficiency [10, 11]. However, this clinical presentation can lead to misdiagnosis in a patient with FVD as observed in our study [12]. The woman with eight miscarriages was referred to a gynecologist who diagnosed her as having idiopathic miscarriage. This caused the patient not to visit a hematologist. Only a bleeding episode led to a referral to a hematologist and the diagnosis of FVD. In fact, miscarriage in patients with RBDs is an alarm for physicians, who should consider it as a presentation of the deficiency. With greater awareness, the rate of miscarriage and related morbidity and mortality may abate [11].

Six of eight women who had one or more miscarriages suggest that FVD should always be considered as a possible cause. An appropriate treatment strategy can result in successful delivery in such patients. Several recent studies provided valuable data [6–8]. The 2006 study conducted by Sanne Velllinge reported a case of homozygous FVD who with adequate prophylactic therapy, delivered a healthy baby [6]. Girolami et al. in a similar study, reported 22 cases (five homozygous and 17 heterozygous) in which administration of fresh frozen plasma yielded an excellent fetal outcome [7]. Connel et al. reported a case with severe FVD that had a successful delivery [13]. In regard to the relatively high rate of FVD, and concomitant rate of miscarriage in Sistan and Baluchestan Province, early diagnosis is crucial to decrease the rate of morbidity and mortality in this cohort. Previous studies on the patients with factor XIII deficiency in this province demonstrated that molecular diagnosis is a reliable and simple method for early diagnosis, carrier detection and prenatal diagnosis; this step can be used equally for patients with FVD to enable them to deliver healthy offspring [14].

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References

1. Kadir R, Chi C. Pregnancy and rare bleeding disorders. Haemophilia. 2009;15(5):990–1005.
2. Naderi M, Tabibian S, Hosseini MS, Alizadeh S, Hosseini S, Shamsizadeh M, et al. Congenital combined deficiency of coagulation factors: a study of seven patients. Blood Coagul Fibrinolysis. 2015;26(1):59–62.
3. Naderi M, Tabibian S, Hosseini MS, Alizadeh S, Hosseini S, Karami H, et al. Rare bleeding disorders: a narrative review of epidemiology, molecular and clinical presentations, diagnosis and treatment. J Pediatr Rev. 2014;2(2):31–46.
4. Naderi M, Tabibian S, Dorgalaleh A, Kashani Kahtib Z, Alizadeh S. Public health problems related to factor V deficiency in southeast of Iran. Med J Islam Repub Iran. 2014;28(1):171–3.
5. Naderi M, Tabibian S, Alizadeh S, Hosseini S, Zaker F, Bamedi T, et al. Congenital factor V deficiency: comparison of the severity of clinical presentations among patients with rare bleeding disorders. Acta Haematol. 2014;133(2):148–54.
6. SanneVellinga ES, IngeVangenechten AG. Successful pregnancy in a patient with factor V deficiency: case report and review of the literature. Thromb Haemost. 2006;95:896–7.
7. Girolami A, Scandellari R, Lombardi A, Girolami B, Bortoletto E, Zanon E. Pregnancy and oral contraceptives in factor V deficiency: a study of 22 patients (five homozygotes and 17 heterozygotes) and review of the literature. Haemophilia. 2005;11(1):26–30.
8. Dorgalaleh A, Naderi M, Hosseini MS, Alizadeh S, Hosseini S, Tabibian S, et al. Factor XIII deficiency in Iran: a comprehensive review of the literature. Semin Thromb Hemost. 2015;41(3):323–9.
9. Naderi M, Dorgalaleh A, Alizadeh S, Tabibian S, Hosseini S, Hosseini MS, et al. Clinical manifestations and bleeding episodes among heterozygote individuals of factor XIII deficiency, a short term prospective study. Blood. 2014;124(21):2852.
10. Naderi M, Dorgalaleh A, Alizadeh S, Tabibian S, Hosseini S, Shamsizadeh M, et al. Clinical manifestations and management of life-threatening bleeding in the largest group of patients with severe factor XIII deficiency. Int J Hematol. 2014;100(5):443–9.
11. Dorgalaleh A, Naderi M, Shamsizadeh M. Morbidity and mortality in a large number of Iranian patients with severe congenital factor XIII deficiency. Ann Hematol. 2016;95(3):451–5.
12. Huang J, Koerper M. Factor V deficiency: a concise review. Haemophilia. 2008;14(6):1164–9.
13. O'Connell M, Eogan M, Murphy K, White B, Keane D, O'Donnell J. Solvent–detergent plasma as replacement therapy in a pregnant patient with factor V deficiency. J Matern-Fetal Neonatal Med. 2004;16(1):69–70.
14. Naderi M, Reykande SE, Dorgalaleh A, Alizadeh S, Tabibian S, Einollahi N, et al. Establishment of a prenatal diagnosis schedule as part of a prophylaxis program of factor XIII deficiency in the southeast of Iran. Blood Coagul Fibrinolysis. 2016;27(1):97–100.