Congenital Factor XIII Deficiency

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13.1 Introduction

Coagulation factor XIII (FXIII) is a transglutaminase (EC 2.3.2.13) composed of two carrier subunits (FXIII-B_2) and two catalytic subunits (FXIII-A_2) which circulates in the bloodstream as a heterotetramer (FXIII-A_2B_2) [1]. FXIII has a crucial role in hemostasis and in the final step of coagulation cascade, with the cross-linking of unstable primary fibrin, makes it firm and stable [1, 2]. In addition to the well-known role of FXIII in coagulation cascade, this factor has several crucial roles in other processes including angiogenesis, wound healing, and pregnancy maintenance as well as bone metabolism and cardiac protection [1, 3–6]. Congenital FXIII deficiency is an extremely rare hemorrhagic disorder with estimated incidence of 1 per 2 million in the general population. Patients with this disorder present severe clinical presentations including umbilical cord bleeding, recurrent pregnancy loss, and intracranial hemorrhage (ICH) [7]. Patients with severe FXIII deficiency (<1%) should receive regular primary prophylaxis from the time of diagnosis, even in the absence of severe clinical presentations. Different therapeutic choices are available for this disorder, including fresh frozen plasma (FFP), cryoprecipitate, FXIII concentrate (Corifact™/Fibrogammin®P), and recombinant FXIII (rFXIII) (NovoThirteen, Tretten) [7–9]. Today FXIII concentrate is the treatment of choice,

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and FFP and cryoprecipitate are not recommended due to the risk of transfusion-transmitted diseases. In addition to primary prophylaxis, these patients may require on-demand therapy in different situations. Dose of replacement therapy in these conditions such as acute bleeding, ICH, and major and minor surgeries varies in case to case. FXIII deficiency is the most underdiagnosed bleeding disorder that accompanies with normal results in routine coagulation tests. FXIII functional assay is recommended as the first-line screening test, but clot solubility test remained as the only diagnostic test in a considerable number of countries [7, 8]. The available used assays for the measurement of FXIII activity are ammonia release assays that can potentially overestimate FXIII activity in the absence of plasma blank [2, 9]. Diagnosis of the disorder can be made based on clinical presentations, family history, and appropriate laboratory diagnosis. With timely diagnosis and appropriate management of the disorder, severe diathesis of the disorder and fetal consequences can be significantly decreased or even be alleviated [2, 8].

13.2 Factor XIII Structure and Function

FXIII or fibrin-stabilizing factor is a 37 kDa circulating protein in plasma as a tetramer ($FXIII\text{-}A_2B_2$) composed of two subunits including catalytic $FXIII\text{-}A_2$ and carrier $FXIII\text{-}B_2$. FXIII-A is mainly synthesized by bone marrow origin cells, while FXIII-B is mainly produced by hepatocytes [2, 10–13]. FXIII-A as a tetramer is present in plasma ($FXIII\text{-}A_2B_2$), while dimeric form of protein ($FXIII\text{-}A_2$) is present in platelets, monocytes, megakaryocytes, and macrophages [12, 13]. About 50% of FXIII-B presents in plasma in dimeric non-complex form [2].

FXIII-A is a 731-amino acid transglutaminase (732 amino acids with initiator methionine) and consists of an activation peptide in the N-terminal and four other domains: β-sandwich, catalytic core, β-barrel 1, and β-barrel 2 (Fig. 13.1) [2, 3].

Activation peptide, composed of first 37 amino acids in N-terminal of FXIII-A, buries cysteine 34 in catalytic core to prevent its access to substrate and keeps FXIII-A in inactivation form [2, 3]. Tyrosine 560 side chain in β-barrel 1 also has a similar function. Therefore, for the activation of FXIII-A, the activation peptide should be cleaved, and tyrosine 560 should be dislocated. This cleavage is done by

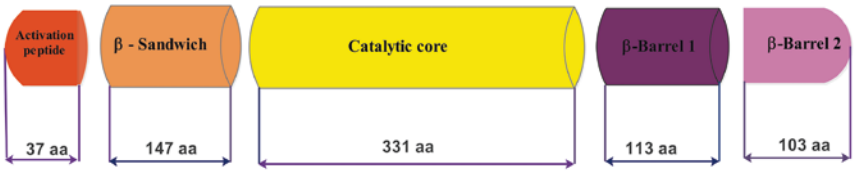

Fig. 13.1 Structure of factor XIII-A subunit. Factor XIII consists of an activation peptide that comprises the first 37 amino acids of the N-terminus, β-sandwich domain (R38–184), the catalytic core domain (R185–515), β-barrel 1 (R516–628), and final domain of factor XIII-A at the C-terminal of the protein β-barrel 2 (R629–731)

thrombin that cleaves between arginine 37 in activation peptide and glycine 38 in β-sandwich. Activation peptide is released in plasma, and this cleavage helps the stabilization of FXIII-A dimer. Cleavage of only one activation peptide is sufficient to complete the activation of FXIII-A_2 (Fig. 13.2) [2, 3].

Finally in the presence of Ca^{2+}, disassociation of FXIII-B and FXIII-A subunits occurs, and FXIII becomes fully activated. Activated FXIII catalyzes an acyl transfer reaction [2, 10].

FXIII-B is a 641-amino acid glycoprotein with a molecular weight of about 80 kDa. FXIII-B is composed of ten short tandem repeats called sushi domains. Each of these domains consists of about 60 amino acids. FXIII-B is carrier of FXIII-A in plasma, and in the absence of FXIII-B subunit, plasma level of FXIII-A subunit significantly is decreased. It seems that sushi one has a crucial role in FXIII-A_2B_2 heterotetramer formation [2, 3].

In addition to the well-known role of FXIII in coagulation cascade, it has several important roles in the body including angiogenesis, wound healing, bone metabolism, cardiac protection, and pregnancy maintenance [2, 3, 10]. FII, FVII, FXIII, and tissue factors all had relatively significant role on angiogenesis [2, 3]. It seems that FXIII performs this role by activation of TGF-β, which is a potent proangiogenic factor, and also by stimulation of neovascularization. Recurrent miscarriage is a common feature of congenital FXIII deficiency [7, 15]. Although the exact process of miscarriage in congenital FXIII deficiency is not known, FXIII accumulates in the placenta in the joining site of maternal and fetus tissues and helps in the cytotrophoblastic shell formation and stabilization of fibrinoid layer. In FXIII-A deficiency, the formation of cytotrophoblastic shell and fibrinoid layer is impaired and leads to placenta detachment and subsequently fetal loss [2, 14].

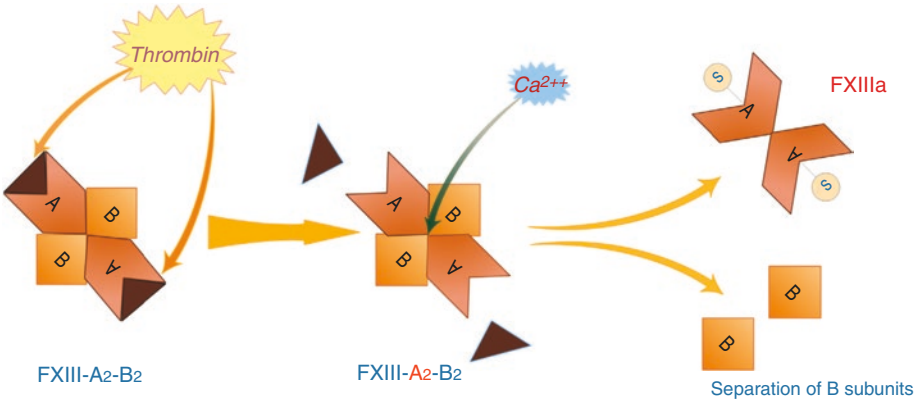

Fig. 13.2 Activation of factor (F) XIII ([2] with permission from publisher). For the activation of FXIII-A, the activation peptide should be cleaved by thrombin that cleaves between arginine 37 in activation peptide and glycine 38 in β-sandwich. Activation peptide is released in plasma and this cleavage helps the stabilization of FXIII-A dimer. In the next step, in the presence of Ca^{2+}, disassociation of FXIII-B and FXIII-A subunits occurs, and FXIII becomes fully activated

Impaired wound healing was reported in 20% of patients with congenital FXIII deficiency. It seems that the main issue which causes impaired wound healing is the impact of FXIII on collagen synthesis and its cross-linking that in some extent is performed by FXIII [5, 16, 17].

13.3 Congenital Factor XIII Deficiency

Congenital FXIII deficiency is an extremely rare hemorrhagic disorder with estimated incidence of 1 per 2 million in the general population. This disorder is inherited in autosomal recessive manner and therefore is more frequent in areas with high rate of consanguineous marriage [7]. Iran, especially southeast Iran, is such area that with high rate of consanguinity has the highest global incidence of this disorder. Patients with congenital FXIII deficiency represent a wide range of clinical manifestations notably umbilical cord bleeding (>80%) in the first days of life. Moreover patients have other life-threatening bleeds including umbilical cord bleeding, ICH, and recurrent pregnancy loss [5, 18]. Other bleeds such as hematoma, hemarthrosis, and epistaxis also can be observed among these patients. Due to the high rate of life-threatening bleeding, timely diagnosis and appropriate management of this disorder are crucial [18, 19]. Diagnosis of this disorder is a challenge worldwide, and FXIII functional assay is recommended as the first-line screening test, but clot solubility test remained as the only diagnostic test in many areas of the world [8, 19–21]. Due to the high rate of ICH in congenital FXIII deficiency, regular primary prophylaxis is mandatory for all severely affected patients from the time of diagnosis, even in the absence of severe clinical presentations. Patients with congenital FXIII deficiency can be managed by FFP and cryoprecipitate, as traditional choices, or by FXIII concentrate (Corifact™/Fibrogammin®P) or recombinant FXIII (rFXIII) (NovoThirteen, Tretten), as new therapeutic options. Due to the risk of transmission of blood-borne diseases with transfusion of FFP and cryoprecipitate, FXIII concentrate is the treatment of choice [18, 22]. But this plasma-derived component is not available everywhere, and in these areas, it is better to use viral inactivated blood component, especially FFP because viral inactivated form of cryoprecipitate is not available [2]. Although FXIII deficiency is

Table 13.1 Classification of factor XIII deficiency

		Plasma FXIII activity	Plasma FXIII-A_2B_2 antigen	Plasma FXIII-A antigen	Plasma FXIII-B antigen	Plt FXIII-A antigen
FXIII-A deficiency	Type I	↓↓↓	↓↓↓	↓↓↓	>30%	↓↓↓
	Type II	↓↓↓	**↓N**	**↓N**	>30%	↓↓↓
FXIII-B deficiency		↓↓	↓↓↓	↓↓	↓↓↓	**N**

accompanied with high rate of morbidity and mortality, with timely diagnosis and appropriate management, life-threatening diathesis can be significantly decreased or even can be alleviated [18, 19]. Based on FXIII functional and antigen assays, FXIII deficiency is classified to FXIII-A type I and type II and FXIII-B deficiency (Table 13.1) [23].

13.4 Worldwide Distribution of Congenital Factor XIII Deficiency

The precise distribution of FXIII deficiency in different geographical areas is not clear, and the exact number of patients, such many other inherited disorders in the world was not determined. Due to complications in diagnosis of disease, especially in areas with less equipped coagulation laboratories as well as lower incidence of bleeding in patients with mild and moderate FXIII deficiency, determining the exact distribution of the disease is difficult [8]. According to the World Federation of Hemophilia (WFH) survey in 2016, the total number of patients with FXIII deficiency was 1553 among 72 countries of the world that covered 90% of the world population. According to this survey, Iran with 593 patients has the largest number of patients with FXIII deficiency worldwide [18, 24]. In our recent study, the more precise number of patients with FXIII deficiency in Iran was determined, and it was clear that Iran has the largest global population of FXIII deficiency, and in Iran, Sistan and Baluchestan Province, southeast of Iran, with 410 affected patients has a great number of patients with FXIII deficiency [18]. Although Iran has the biggest population of FXIII deficiency, according to the WFH survey, the United States with 103 affected patients, has a large number of patients with FXIII deficiency (Fig. 13.3).

In a recent report of PRO-RBDD from 52 hemophilia treatment centers (HTCs), data of 573 patients with FXIII deficiency was released. In fact, due to the high number of precipitate countries in this project, this international network gives us some information about prevalence and distribution of the disease worldwide, although other main aims of the study are about frequency of bleeding episodes and management of bleeding and establishment of minimum coagulant activity level to prevent bleeding [24, 25]. In a worthwhile study, on 104 patients with FXIII deficiency with 24 nationalities living in 15 countries, an isolated Finnish population with an incidence of 1 per 650,000 inhabitants has the highest rate of FXIII deficiency in Europe. This high prevalence of FXIII deficiency in Finland was reported previously and has been attributed to be a consequence of the founder effect [26, 27]. According to the investigation of Vytautas Ivaskevicius et al., Switzerland had a prevalence of 14 unrelated families per 7.4 million inhabitants and Poland had 1 case per 6,000,000 residents (total population of 38 million) [27].

Fig. 13.3 The number of patients with congenital factor XIII deficiency in different countries. World Federation of Hemophilia (WFH) 2016 survey

13.5 Clinical Manifestations

Congenital FXIII deficiency is one of the most serious and severe congenital bleeding disorders with very high rate of life-threatening bleeding diathesis. Umbilical cord bleeding with a frequency of >80% is the most common presentation of congenital FXIII deficiency. This presentation is also frequent in congenital afibrinogenemia (~85%) [27–29]. Umbilical cord bleeding is a medical emergency that requires medical intervention [19, 29]. ICH is another severe presentation of congenital FXIII deficiency that is more frequent in this disorder than any other congenital bleeding disorder [19, 30]. The prevalence of ICH in congenital FVII, FXD, FVD, and FVIII deficiencies and afibrinogenemia is 15%, 7%, 5%, 4%, and 2%, respectively [30–32]. This diathesis, rarely, was reported in FII deficiency, von Willebrand disease (VWD) type 3, Glanzmann thrombasthenia, and gray platelet syndrome [32–37]. Without timely diagnosis and appropriate management of patients with congenital FXIII deficiency, ICH leads to death of about one third of patients with this disorder until the middle age [19, 30, 38]. ICH is the cause of 80% of death in congenital FXIII deficiency and in 15% of cases who experience this diathesis results in death [19]. Miscarriage is another common presentation of women with congenital FXIII deficiency. This presentation can be observed in both FXIII-A and FXIII-B deficiencies. The frequency of miscarriage is about 15% in FXIII-B deficiency, while this diathesis is more common in FXIII-A deficiency. Although, rarely successfully delivery can be observed in FXIII-A deficiency

without replacement therapy, generally it is accepted that without replacement therapy unable to have successfully delivery [8, 14, 39, 40]. Different clinical presentations of patients with congenital FXIII deficiency according to four main studies were summarized in Table 13.2.

13.6 Molecular Basis

FXIII-A_2B_2 is encoded by two separated genes on 6p24–25 (FXIII-A subunit) and 1q31–32.1 (FXIII-B subunit) chromosomal regions. *F13A1* and *F13B* genes have 15 and 12 exons, respectively. A wide spectrum of normal gene variations was observed throughout two genes [41, 42]. Five common polymorphisms were observed in *F13A1* gene including Val34Leu, Tyr204Phe, Pro564Leu, Glu651Gln, and Val650Ile. Val34Leu polymorphism as the most common polymorphism is common among different populations except for Asian [2, 42]. Two common polymorphisms were reported in *F13B* gene including His95Arg and IVS11+144 (nt29756 C > G). In addition to these normal gene variations, a wide range of disease-causing mutations was observed in *F13A1* gene, while only 16 mutations were observed in *F13B* gene. A total of 156 mutations, mostly missense, were observed within *F13A1* gene [1, 43, 44] (Fig. 13.4).

These mutations are scattered throughout *F13A1* gene and mostly are specific to an especial family or ethnicity. Trp187Arg (c.559T>C) (according to HGVS: Trp188Arg, c.562 T>C), as the most common mutation of *F13A1* gene, only was

Table 13.2 Clinical manifestations of patients with congenital factor XIII deficiency

	Dorgalaleh et al (*n*: 190) (%)	Lak et al. (*n*: 93) (%)	Shetty et al. (*n*: 96) (%)	Ivaskevicius et al. (*n*: 104) (%)
Umbilical cord bleeding	82.5	73	73	56
Hematoma	53	58	–	49
Prolonged wound bleeding	31	–	–	–
Gum bleeding	17	48	13	–
Epistaxis	14	32	25	–
Ecchymosis	13	–	58	–
GI bleeding	–	10	–	6
Delayed postdental extraction bleeding	7	–	–	–
Intracranial bleeding	17	25	19	34
Post-circumcision bleeding	4	–	–	–
Hemarthrosis	4	55	7	36
Postsurgical bleeding	3	84	19	40
Miscarriage	10[a]	50	–	–
Menorrhagia	5	10	94	–

observed in a large number of Iranian patients. IVS5–1G>A and c.1984C>T were observed among different European countries [27, 41, 44]. c.1984C>T was also observed in Korea and India [45–47]. These mutations can be used for prenatal diagnosis (PND), in affected families. Trp187Arg, as the only disease-causing mutation of *F13A1* gene in southeast Iran, routinely is used for diagnosis of patients, pre-marriage and PND [2, 41, 44]. Most of *F13A1* gene mutations cause FXIII protein insatiability and intracellular degradation [2, 41, 44].

13.7 Diagnosis

Since FXIII deficiency is an autosomal recessive disorder with severe bleeding tendency, diagnosis of disorder could be made based on family history, clinical presentations, and an appropriate laboratory approach [8]. Diagnosis of congenital FXIII deficiency is a challenge worldwide, and FXIII deficiency is on of the most underdiagnosed bleeding disorders. In patients with congenital FXIII deficiency, all routine coagulation tests including prothrombin time (PT) and activated partial thromboplastin time (aPTT), thrombin time (TT), and bleeding time (BT) are normal, unless concomitant coagulopathy is present. For example, in systemic lupus erythematosus with lupus anticoagulant, both prolonged aPTT and decrease FXIII level due to autoantibody against FXIII may be present [2, 48]. Traditionally, clot solubility test is used for diagnosis of FXIII deficiency. Although clot solubility test is not further recommended for diagnosis of FXIII deficiency, a considerable number of laboratories over the world use this test as the only diagnostic test for detection of FXIII deficiency [7, 8, 49]. In this assay, patient's plasma is incubated with calcium with or without thrombin for 1 hour at room temperature (RT) or 37 °C. Then clot is suspended in a solubilizing agent most often urea 5M, acetic acid 2%, or monochloroacetic acid (MCA) 1% and incubated at 37 °C or RT, and then it is evaluated in regular intervals of 20 min, 1 h, and 24 h. In patients with FXIII deficiency, clot is dissolved within a few minutes to 1 h, while in normal individuals, clot is stable for 1 day or more [20].

Sensitivity and specificity of clot solubility test are affected by clotting agent and solubilizing agent. Although there are more sensitive combinations of clot solubility test including the combination of thrombin as clotting agent and acid acetic 2% as solubilizing agent, one of the least sensitive combinations and one of the most commonly used method worldwide includes urea 5M as solubilizing agent and calcium chloride as clotting agent. These common combinations are sensitive to 1–5% of plasma FXIII, while combination of thrombin and acetic acid is sensitive to 10% [20, 8]. Other combinations, such as calcium chloride with acetic acid and thrombin with urea, were reported to have intermediate sensitivity. Severe bleeding may occur even in the absence of abnormal clot solubility test. Since, clot solubility test is a qualitative assay, with low sensitivity and specificity, and is a poorly standardized test that can be affected by several factors including clotting agent, solubilizing agent, and fibrinogen concentration, FXIII and Fibrinogen subcommittee of the International Society on Thrombosis and Hemostasis (ISTH) recommended a

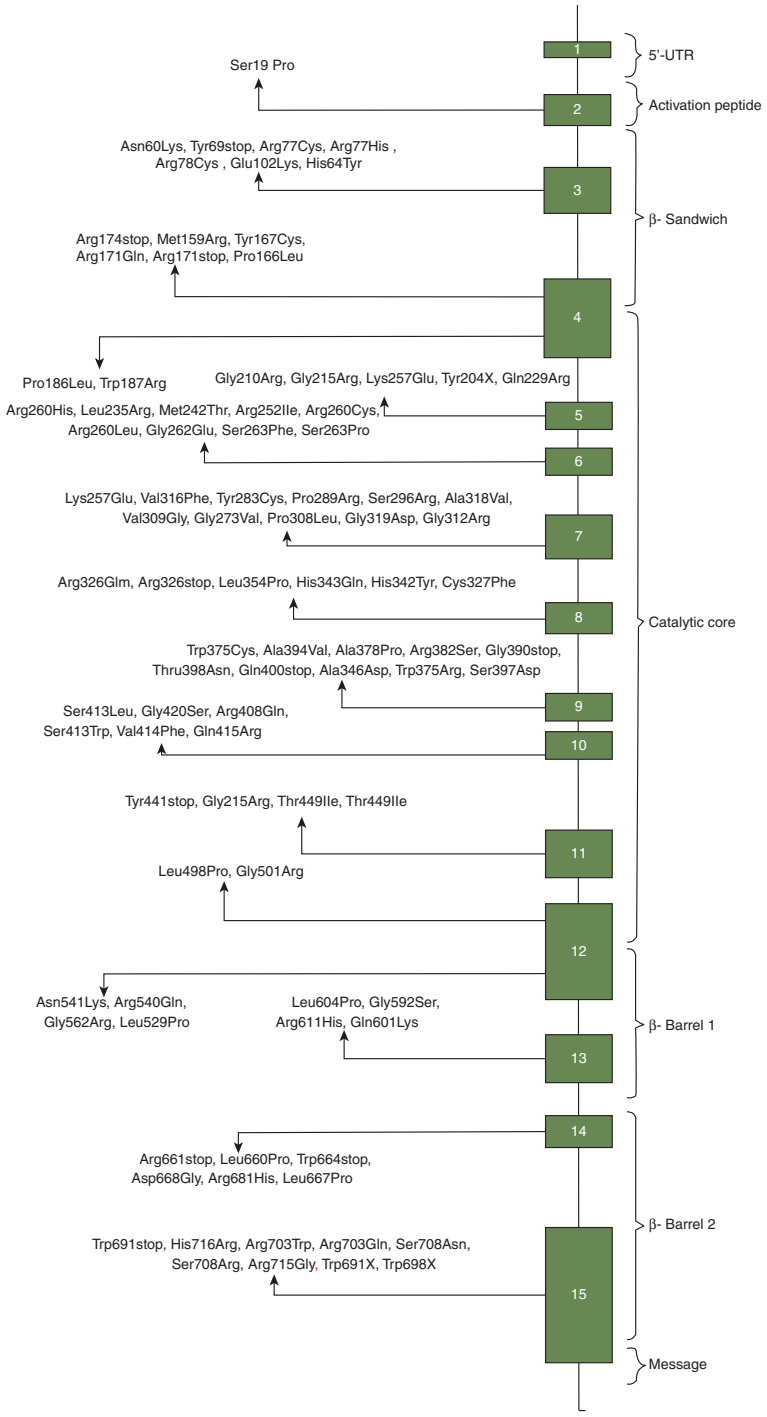

Fig. 13.4 *F13A1* gene missense mutations

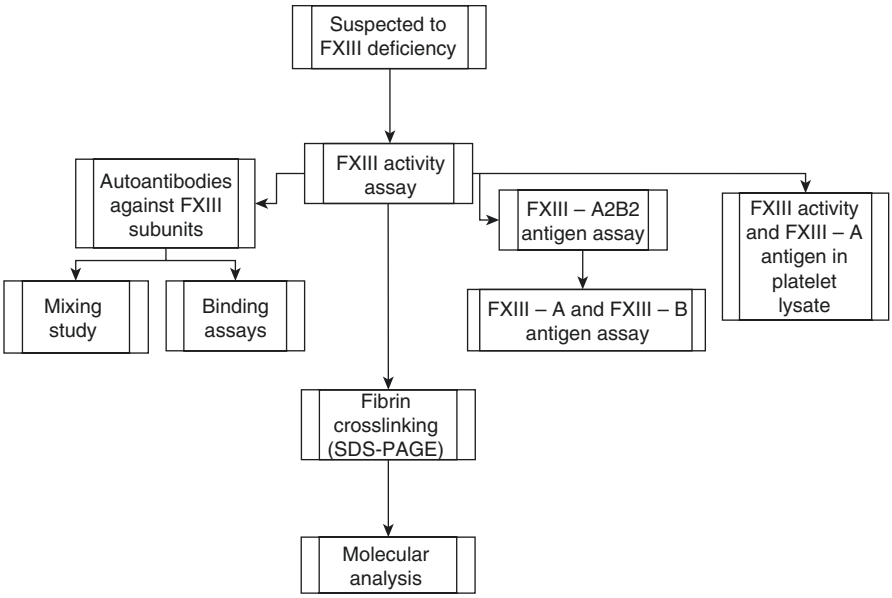

Fig. 13.5 International Society on Thrombosis and Hemostasis (ISTH) recommended algorithm for diagnosis and classification of factor XIII deficiency. factor XIII functional activity assay is recommended as the first-line screening test. If plasma factor XIII activity is decreased, the subtype of disorder can be determined by the measurement of plasma factor XIII-A_2B_2 antigen assay and measurement of FXIII activity and FXIII-A antigen in platelet lysate. If factor XIII-A_2B_2 antigen level is decreased, factor XIII-A_2 and factor XIII-B_2 should be measured. If the presence of inhibitor is suspected, mixing study for detection of neutralizing antibodies against factor XIII-A should be performed. For detection of non-neutralizing antibodies against factor XIII-A and factor XIII-B, binding assays should be done. For further evaluation of disorder, assessment of fibrin cross-linking by SDS-PAGE can be performed. Molecular analysis can be performed for final confirmation of the disorder

reliable algorithm for diagnosis and classification of FXIII deficiency. According to this algorithm, FXIII functional assay is recommended as the first-line screening test (Fig. 13.5) [23].

13.7.1 Factor XIII Functional Assay

Different methods were introduced for FXIII functional assay, including photometric assay, incorporation assay, and fluorometric assay. Each of these methods has some advantages and disadvantages; familiarity with these issues can help to have a proper and precise diagnosis of the disorder [2, 8, 50]. Several commercial kits are available based on these methods. Available FXIII functional assays are based on the measurement of end products of FXIII transglutaminase activity including the measurement of (1) ammonia released from a glutamine-containing substrate, (2) a

substrate amine incorporated into a substrate protein, and (3) assessment of fibrin cross-linking. The ammonia release assays are the only available commercial FXIII functional assays [8, 23, 50]. These kinds of assays are quick, user friendly, and kinetic and can be used on coagulometer. One of the most common available photometric assays is Berichrom FXIII assay (Dade Behring, Marburg, Germany). In photometric assay, FXIII is activated by thrombin and calcium during lag phase of reaction, and transglutaminase activity of FXIII is measured [2, 20, 50]. In first step of reaction, FXIII catalyzed and acyl transfer reaction. In this reaction, carboxamide group of peptide-bound glutamine residue is acyl donor. It forms a thioacyl complex with the –SH group Cys314 of FXIII active site and ammonia is released [20]. In the second step of reaction, the thioester is broken, and the acyl acceptor primary amine through a peptide bond is bound to the glutamyl residue. Finally, released ammonia is measured. This measurement in Berichrom FXIII assay, is NADH, and in REAchrom assay is a NADPH-dependent glutamate dehydrogenase (GlDH) reaction, and the rate of decrease of NADH or NADPH absorbance measured at 340 nm is directly proportional to the catalytic amount of FXIII (Table 13.3) [20, 50–52].

One of the most important point about ammonia release assay is the potential significant overestimation of FXIII activity between 2% and 14% without plasma blank that is more important in the low level of FXIII [8, 52, 53]. To overcome this problem, plasma blank is used in which an irreversible FXIII active site inhibitor such as iodoacetamide is used, and the obtained value from this blank is subtracted from the measured FXIII activity of the sample [8, 52–55]. Another problem with ammonia release assay is low sensitivity. In order to improve the sensitivity of this assay, it was recommended to increase plasma: reagent ratio and prolong measurement intervals [20].

13.7.2 Factor XIII Antigen Assay

FXIII antigen assay can be used for classification of FXIII deficiency. In most common type I of FXIII-A deficiency, concomitant decrease is observed in both FXIII activity and antigen assays, while in type II, FXIII antigen level is in normal range. With available commercial kits, FXIII-A, FXIII-B, and FXIII-A_2B_2 antigens can be measured [8, 20]. Reference interval of FXIII-A_2B_2 antigen is between 67% and 133%, and this range for FXIII activity is between 67% and 143% [2, 20]. Activity and antigen assays also can be performed on platelet lysate. Enzyme-linked immunosorbent assay (ELISA) is one of the most sensitive and reliable methods for the measurement of FXIII antigen level [19, 54]. According to Clinical and Laboratory Standards Institute (CLSI) guidelines, these three points should be considered for FXIII antigen assay [8, 54]:

(1) Non-complex FXIII-B should not interfere with FXIII-A_2B_2 antigen assay.
(2) When subunit assays are performed, both free and complex antigenic forms should react with anti-FXIII subunit antibodies with the same extent.
(3) Used assay should not be interfered by fibrinogen concentration.

Table 13.3 Qualitative and quantitative assays for diagnosis of factor XIII deficiency

Assay	Clotting	Solubilizing	Detection limit (%)	Advantage	Disadvantage
Clot solubility test	Thrombin	Acetic acid	10	1. Sensitive 2. Rapid	Low specificity
	$CaCl_2$	$CaCl_2$	0–3	1. Rapid 2. Easy	Low sensitivity
	$CaCl_2$	Urea	3–5	1. Rapid 2. Easy	No consensus about the sensitivity
Functional assay	Available kit	Country			
Amine release assays	Berichrom assay	Germany	<5	1. Quick 2. One-step kinetic 3. Easily automated 4. Good reproducibility	Low sensitivity
	REA-chrom assay	Hungary	<3		
	Technochrom assay	Austria	<5		
Amine incorporation assays	Commercial kit is not available but used in research and specialized laboratories			1. Highly sensitive	1. Time-consuming 2. Not automated 3. Poorly standardized 4. Affected by Val34Leu polymorphism

13.8 Management

13.8.1 Prophylaxis

Regular primary prophylaxis is mandatory for all patients with severe congenital FXIII deficiency, from the time of diagnosis, even in the absence of severe clinical presentations. The main reason for this decision is the high rate of life-threatening bleeds, notably ICH. Different choices were used for treatment of congenital FXIII deficiency, including whole blood (WB), FFP, and cryoprecipitate. Although, now, FXIII concentrate (Corifact™/Fibrogammin®P) and rFXIII (catridecacog, NovoThirteen, Tretten). A significant number of countries over the world only can use FFP and cryoprecipitate, most often due to economic affairs [56–62]. The main concern with regard to use of FFP and cryoprecipitate is the risk of transfusion-transmitted infectious. In spite of these issues, use of FXIII concentrate is growing, and today this plasma-derived component is the treatment of choice. It was accepted that for prevention of major bleeding, plasma FXIII level should be kept above 5%, and to remain patients asymptomatic, a goal of 10% of FXIII is desirable [58–61].

Although several prophylaxis programs were introduced, two main strategies are 10 IU/Kg FXIII concentrate (Fibrogammin P; CLS Behring, Marburg, Germany) and 40 IU/kg (Corifact; CLS Behring, Marburg, Germany) every 4 weeks [2, 56, 60, 63]. The first one was successfully used for a long time in a large number of Iranian patients with congenital FXIII deficiency. This regimen significantly reduces the rate of minor bleeds and deviates major bleeds. In the latter program, incidence of minor bleeds was lower than the former. In addition to prophylaxis dose of FXIII concentrate, patients may require on-demand treatment that means stopping of bleeding as soon as possible after onset of bleeding. These include treatment and management of acute bleeding, ICH, and dental management as well as successful delivery and major and minor surgeries [57, 63].

13.8.2 Management of Intracranial Hemorrhage

ICH is the most dreadful complication and the main cause of morbidity and mortality among patients with congenital FXIII deficiency. In addition to ICH, these patients may rarely experience extracranial hemorrhage (ECH) (~5%). ICH is the most common in congenital FXIII deficiency than any other congenital bleeding disorder [30]. Although the incidence of ICH is about 30%, as high as 60% were reported in neonatal period [30, 63]. Post-traumatic ICH is more frequent in neonatal period, while spontaneous ICH is more common in adults [19]. About one fifth of patients experience this diathesis recurrently in the absence of appropriate replacement therapy. The most common site of ICH is intraparenchymal (>90%), while subdural and epidural hemorrhages are rarely seen [30]. ICH is the main cause of death in congenital FXIII deficiency, and 80% of deaths are attributed to this life-threatening diathesis. ICH, in 15% of patients, leads to death, while in the majority of patients, it causes neurological complications. Although ICH is a very severe presentation of congenital FXIII deficiency, with timely diagnosis and appropriate management, the incidence of this diathesis can significantly decrease. Primary prophylaxis is very effective in preventing ICH, but traumatic ICH can occur even in patients under prophylaxis. For patients undergoing ICH, timely diagnosis is the key step to decrease debilitating consequences [19]. In patients with congenital FXIII deficiency with signs and symptoms of cranial hemorrhage including headache, vomiting, loss of consciousness, and visual disturbance, replacement therapy should be considered even before establishment of diagnosis [30, 64–66]. The mainstay of treatment of ICH in FXIII deficiency is replacement therapy, while the role of neurosurgery remained controversial. For patients with ICH, plasma FXIII level should be kept in normal range for at least 2 weeks. For this purpose, up to an alternate day dose before reducing replacement therapy to routine prophylaxis program may be required [30]. ICH leads to different neurological complications, including locomotor disability, mental disorders and visual disturbance, hearing problems, and speech and psychological impairments. Locomotor disability and psychological disabilities are the most common. Some of these patients experience severe neurological complications such as hemiplegia that

disrupt their normal lifestyle. Due to the high rate of neurological complications, long-term neuropsychological evaluations should be considered for patients with congenital FXIII deficiency and ICH [19, 30, 67, 68].

13.8.3 Successful Delivery

Pregnancy loss is one of the main complications of women with congenital FXIII deficiency. This complication is more frequent in FXIII-A deficiency than FXIII-B deficiency. Reported frequency of pregnancy loss is between 30% and 100% for FXIII-A deficiency and 15% for FXIII-B deficiency, respectively. Although successful delivery without replacement therapy was observed among women with congenital FXIII deficiency, generally it is accepted that women with severe congenital FXIIID (<1%) are unable to have successful delivery without replacement therapy. These patients may experience recurrent pregnancy loss in the absence of replacement therapy, while appropriate management can lead to successful delivery in about all women (Fig. 13.6) [39, 69–73].

For successfully delivery, plasma FXIII level should be kept higher than 10%. Several strategies have been proposed for successful delivery. For instance, it was recommended that women get 250 IU FXIII concentrate (Corifact™/Fibrogammin®P) during the first 22 weeks of gestation and then 500 IU and finally 1000 IU before labor [39]. Another strategy successfully used on a large number of women is the administration of 10 IU/kg Fibrogammin P (Dade Behring, Marburg, Germany) every 4 weeks as routine prophylaxis, then 10 IU/kg every 2 weeks during pregnancy, and finally 10 IU/kg before labor [56, 72, 73].

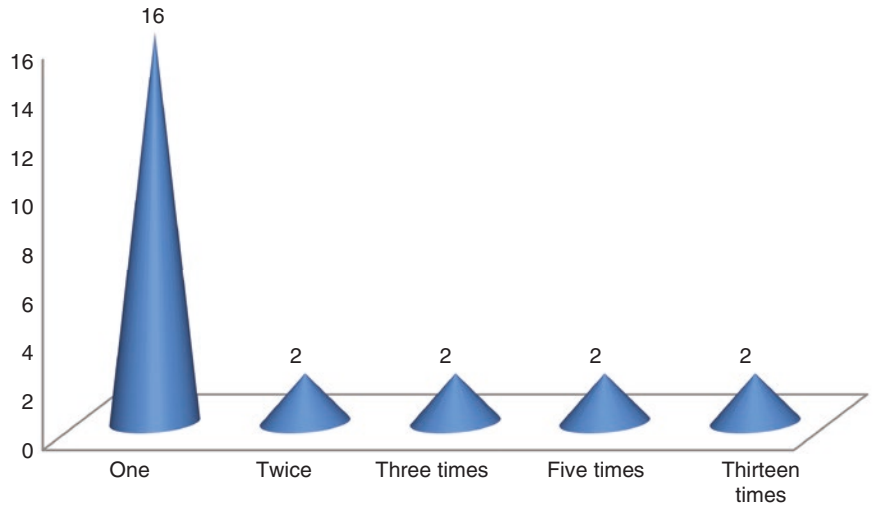

Fig. 13.6 Number of miscarriage in a study on the large number of women with congenital factor XIII deficiency

13.8.4 Management of Major and Minor Surgeries

Management of surgery is a challenge in congenital FXIII deficiency, and even a minor invasive procedure can lead to severe life-threatening hemorrhage. According to the United Kingdom Haemophilia Centre Doctors' Organization guideline [73–75]:

1. For minor surgery consider tranexamic acid 15–20 mg/kg or 1 g four times daily alone.
2. For major surgery, consider additional FXIII concentrate 10–40 IU/kg depending on the interval since the last prophylaxis and severity of bleeding.

Although it was also recommended that for major surgeries, patients should receive higher dose to keep plasma level higher than 5%, recent studies proposed more suitable recommendations. Patients should receive replacement therapy immediately before surgery [73, 74].

It was recommended to have a replacement therapy administrated immediately before surgery. For major surgeries, plasma FXIII level should increase to 50% before procedure, and in sophisticated and prolonged surgeries, plasma level of FXIII should increase to 100%. But even a FXIII level of 100% can not grangtee prevention of hemorrhge. For surgery, especially major and sophesticated surgeries, all steps of surgery should be performed with close monitoring of patients durring surery. It should kept in the mind that a unique protocol can not be used for all patients with FXIII deficiency and several factors can affect management of surgery. These factors including kind of surgery, durriation and complication of surgery. A suitable therpeutic therapeutic dose not only should lead to a safe surgery but also provoke normal postsurgery wound healing. In fact, for management of a surgery in congenital FXIII deficiency, all issues including the type and duration as well as complication of surgery should be considered [59, 75].

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