

## Review Article

## Burden of Congenital Factor XIII Deficiency in Iran

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### Abstract

Congenital factor XIII (FXIII) deficiency is a rare coagulopathy with the highest incidence in Iran. Iranian patients with FXIII deficiency (FXIIID) presented high rate of bleeding episodes, some of them are major cause of disability and mortality among these patients. Hemarthrosis and intracranial hemorrhage (ICH) can affect activity and social productivity of patients. ICH, recurrent miscarriage and umbilical cord bleeding are the major cause of mortality. Hematoma, and prolonged menstrual bleeding as well as post-surgical bleeding are other significant bleeding in Iranian patients with FXIIID. Present of severe life threatening bleeding episodes and other notable bleedings, can significantly reduce working activities and social productivities of patients. Although Iranian patients with FXIIID, experienced significant diseases related complications, early diagnosis accompany by appropriate therapeutic regimes can prevent most of these problems.

**Keywords:** Factor XIII deficiency, Burden, Morbidity, Mortality, Bleeding

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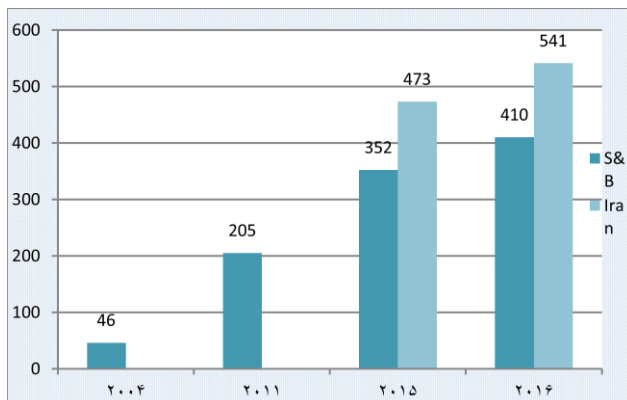
### Introduction

Coagulation factor XIII (FXIII) is a fibrin-stabilizing transglutaminase which strengthens fibrin clot mechanically by cross-linking fibrin chains. In addition, it protects newly formed fibrin from the activated fibrinolytic system by binding 2-plasmin inhibitor to the fibrin meshwork (1). Congenital FXIII deficiency (FXIIID) is an extremely rare but significant bleeding disorder with a prevalence of 1 per 2 million in the general population (2, 3). Patients with severe deficiency, present high rate of life threatening bleeding, including umbilical cord bleeding (UCB), recurrent pregnancy loss and intracranial hemorrhage (ICH) (4, 5). ICH is the major cause of death among these patients and it is more common in FXIIID in comparison to other rare bleeding disorders (RBDs) (6). UCB is the most

common bleeding lead to diagnosis of disorder. This bleeding is also common in fibrinogen disorders (7). Diagnosis of the FXIIID is commonly performed based on clinical presentation, family history as well as appropriate laboratory tests (8, 9). Clot solubility test is a quantitative and low sensitive diagnostic test which is most commonly used for detection of FXIIID. This diagnostic test is not further recommended by experts for diagnosis of disorder. However, a functional assay is recommended as first screening test (3, 10, 11). Management of the disorder is made traditionally by fresh frozen plasma, cryoprecipitate and today by FXIII concentrate (Fibrogammin P) (1, 3).

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Since this disorder is transmitted in autosomal recessive manner of inheritance, it is more common in



**Figure 1.** Prevalence of factor XIII deficiency in Iran.

areas with high rate of consanguineous marriages (12). Iran as a Mideast country with high rate of consanguineous marriage has high prevalence of FXIID. With 483 patients, Iran has about one fourth of world patients with FXIID (2). This high spread of disorder leads to high rate of morbidity and mortality among Iranian patients. The main cause for this high rate of morbidity and mortality among Iranian patients is low equipped coagulation laboratory and therefore nonspecific diagnostic tests in areas with high prevalence of FXIID (8). In addition, little to low diagnostic tools, long distance with health care centers and low economic situation of affected families are other factors lead to this high rate of morbidity and mortality. In the recent years, the number of affected patients continuously is increased (2, 8). In southeast of Iran, as hot spot of disease, the number of affected patients is increased from 46 in 2004 to 205, 352, 410 in 2011, 2015 and 2016 respectively. The numbers of affected patients in Iran, exception of southeast areas, were 121 and 131 in 2015 and 2016, respectively (Figure 1) (2). 11 different mutations are observed in 366 Iranian patients with FXIID. Trp187Arg, observed only in Iran, is the leading cause of FXIID in this country (13).

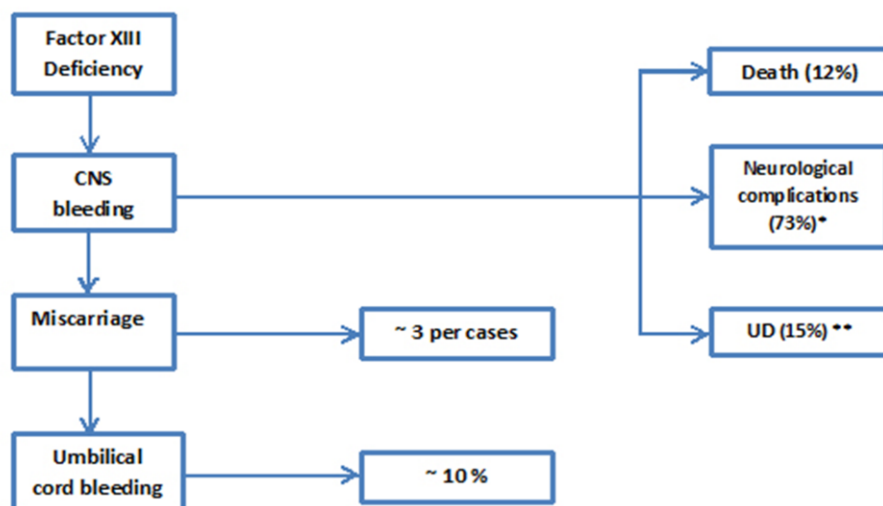
**Burden of factor XIII deficiency in Iran**

The high risk of severe bleeds and ICH in patients with FXIID is likely to result in a high level of physical, psychological and financial burden (5). Although the number of patients was significantly increased, but clot solubility test remains as the only diagnostic test for FXIID. Clot solubility test has low sensitivity and it is just positive in severe FXIID (10). Among patients in southeast of Iran, Khash city

has the highest incidence of disease where there is not any comprehensive coagulation laboratory. Consequently, patients had to travel to Zahedan as provincial center, even for early diagnosis of disorder with clot solubility test. Since considerable numbers of patients in Khash are resident of rural areas with low economic situation, this travel is expensive for them. Moreover, the only hemophilia center of Sistan and Baluchestan province is located in Zahedan city. In fact, all diagnostic and health care facilities are located in the Zahedan as provincial center. This issue is a problem for early and timely diagnosis of disorder and can lead to high rate of morbidity and mortality among these patients (4, 8).

UCB, the most common clinical manifestation, which has reported in 80% of Iranian patients, occurs in early of life. Although this kind of bleeding is a major life threatening bleeding, it easily could be managed with early diagnosis of FXIID. Overall, it is a medical emergency that requires timely medical interventions (2, 8). In a study on 317 patients with FXIID, 221 (69.7%) UCB was observed, that led to death in 21 neonates (~10%) (Figure 2) (8, 14).

In addition, to UCB, ICH is another risk factor for patients with FXIID, which leads to high rate of mortality and related complications. Occurrence of CNS bleeding (CNSB) in pediatric patients with FXIID causes different types of neurological complications including behavioral and developmental disorders as well as hemiplegia and aphasia (3, 15). The kind of CNSB in 95 patients with FXIID was determined; in 91 cases (95.8%) and 4 cases (4.2%) were ICH and extracranial hemorrhage (ECH), respectively. According to a report on age in at the time of CNSB, about one third of patients experienced CNSB in the first two years of life. A number of these patients with FXIID, experienced CNSB following minor trauma but most of them experienced this complication spontaneously. In Sistan and Baluchestan province, with high rate of FXIID, different types of complications reported which not observed in other areas of the world (8). Each of these complications required an urgent medical decision. As we have observed, one of the major complication among neonates with FXIID, following to a normal vaginal delivery is ICH. Neonates with FXIID following the delivery and the



**Figure 2.** This flow chart illustrates prevalence of mortality in factor XIII deficiency. There are three life threatening complications that lead to mortality in FXIID: 1.CNS bleeding 2.misscariage 3.umbilical cord bleeding.

\* 73% of patients with CNS (central nervous system) bleeding show neurological complications instead of death.  
 \*\*UD: undetermined.

stress of passing through delivery canal experience CNSB. In fact, in this traditional society, most of mothers prefer to deliver their child in a normal vaginal delivery. To deal with this problem a prenatal diagnosis (PND) program was established in this area and parents were assessed for Trp187Arg mutation of FXIII-A gene (4, 16). This was the only reported disease resulted from mutation in the gene of FXIII in this area. Almost all of patients in southeast of Iran were homozygote for this mutation (13). Out of 317 patients, about half of them (~46%) were experienced ICH. About two-third (~73%) of them experienced neurological complications and one-third were died (Figure 2) (8). Some of these neurological complications are severe and disruptive of routine life style of the patients. Other CNSB related complications can significantly reduce social communications and activities of patients. Since ICH can occurred spontaneously of post trauma, patients with severe FXIID, should be cautious about their routine activities. In fact, ICH is a major obstacle for normal social activity and major cause of disability in patients with FXIID (2).

Other significant complication of FXIID is miscarriage. Some studies reported that without

appropriate prophylaxis regimes, there is not any woman with severe FXIID who has a successful delivery. Therefore, with a suitable replacement therapy, almost all women with this complication, can have a successfully delivery. Recurrent miscarriage is a very important FXIID related complications and has high rate of mortality (16). Among 24 women with FXIID, a total of 62 miscarriages were observed which revealed nearly three times abortions for each mother (Figure 2) (8). In addition to morbidity and mortality effects of miscarriage and recurrent miscarriages, it has emotional effects on families with FXIID too, especially on affected mother. Sometimes, this severe complication of FXIID has crucial social consequences in affected families (16).

In addition to these complications, other bleedings among patients with FXIID can affect their activity and social productivity. Hematoma, hemarthrosis, prolonged menstrual bleeding, muscle and subcutaneous soft tissues hemorrhages, as well as post-surgical bleeding are other bleeding symptoms among these patients, which could affect their physical health and optimal activity. With timely diagnosis of FXIID and appropriate therapeutic regimes, most of these bleeding and related morbidity

and mortality can be prevented (4, 9).

## Conclusion

Congenital FXIID is a rare but very severe bleeding disorder accompanied by high rate of life threatening bleeds. ICH, recurrent miscarriage and umbilical cord bleeding are the main cause of morbidity and mortality among these patients that imposed high rate of disease burden to health care system. Although the disorder is accompanied by high rate of life threatening bleeds, timely diagnosis and appropriate management of disorder can be eliminated or significantly decreased.

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## Conflicts of Interest

The authors declare that there are no conflicts of interest.

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