REVIEW

WILEY | ISLH International Journal of Laboratory Hematology

Prenatal diagnosis in rare bleeding disorders—An unresolved issue?

S. Tabibian[1] | M. Shams[2,1] | M. Naderi[3] | A. Dorgalaleh[1] iD

[1]Department of Hematology and Blood Transfusion, School of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran

[2]Department of Medical Laboratory, Faculty of Paramedical Sciences, Babol University of Medical Sciences, Babol, Iran

[3]Genetic Research Center in Non-Communicable Disease, Zahedan University of Medical sciences, Zahedan, Iran

Correspondence
Akbar Dorgalaleh, Department of Hematology and Blood Transfusion, School of Allied Medical Sciences, Iran University of Medical Sciences, Tehran, Iran.
Email: dorgalaleha@gmail.com

Abstract

Intracranial haemorrhage (ICH) is the most dreadful complication, and the main cause of death among patients with rare bleeding disorders (RBD) and prenatal diagnosis (PND) is a preventative lifesaving program. A total of 39 PNDs were reported in the literature through a search on PubMed, EMBASE, SCOPUS and Web of Science databases, most often for congenital factor (F) XIII and FVII deficiencies and rarely in FX, FV deficiencies and afibrinogenemia. The main cause to request a PND is ICH and related morbidity and mortality. Different molecular methods including direct sequencing and linkage analysis as well as polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) for a specific mutation are the most common used methods for PND, while factor assay and combination of molecular and factor assay also were used. In this research, 7 severely affected foetuses were identified during PND including 3 foetuses with FXIII deficiency, 3 with FVII deficiency and 1 with FX deficiency. Out of these 7 cases, intrauterine ICH occurred in 1 case with FXIII deficiency, 1 was electively aborted and 1 case with severe FVII deficiency received intrauterine factor transfusion. Postdelivery ICH was reported for 1 patient with severe FVII deficiency within the first month of life. All other pregnancies were uneventful.

KEYWORDS
intracranial haemorrhage, morbidity, mortality, prenatal diagnosis, rare bleeding disorders

1 | INTRODUCTION

Rare bleeding disorders (RBD) account for 3%-5% of all inherited coagulation factor deficiencies, including deficiencies of coagulation factors I (fibrinogen), factor (F) II, FV, combined FV and FVIII, FVII, FX, FXI, FXIII and congenital deficiency of vitamin K-dependent clotting factors (VKCFD). These disorders most often inherited in autosomal recessive manner, except for some cases of FXI deficiency (FXID) and FID. Prevalence of RBD varies from 1 per 300 000 to 500 000 for FVIID to 1 per 2 million for FXIIID and FIID.[1] Bleeding tendency significantly varies between these disorders, and most patients with combined FV-FVIIID (CFV-VIIID) and FVD have mild bleeding and patients

with FXID bleeds only after trauma or surgery but most patients with FXIIID have severe life-threatening bleeding.[2,3] Intracranial haemorrhage (ICH) as the most dreadful and the main cause of death among patients with RBD is commonly observed in congenital FXIIID. About one-third of these patients without appropriate prophylaxis treatment experience this diathesis.[4] ICH was less frequently reported in FVIID, FID and FXD, and rarely was observed in FIID and FVD.[5] Although ICH is the main cause of morbidity and mortality, timely diagnosis and appropriate management of these bleeding disorders can significantly reduce the rate of ICH and related adverse consequences.[4,5] In severely affected patients with RBD, ICH most often spontaneously occurred early in life. This presentation can occur intrauterine, immediately after

birth or during labour due to the stressful condition of delivery.[2,6-9] For such families, prenatal diagnosis (PND) can be a lifesaving diagnostic protocol, which leads to a timely diagnosis, suitable precautions and appropriate management of patients with RBD and high-risk life-threatening bleeding. Here, available data about PND in RBD were reviewed to make a primary background in this setting.

2 | STRATEGY OF SEARCH

In this study, data were obtained from previous studies. As there were a few studies in this area, the reports were found easily. A research was performed on databases of PubMed, EMBASE, SCOPUS and Web of Science during 1980 to 2017. The search terms included the combination of prenatal diagnosis or PND with rare bleeding disorder/RBD,

factor I/FI/fibrinogen deficiency, factor II/FII/F2 deficiency, factor V/ FV/F5 deficiency, combined factor V and factor VIII/FV and FVIII/ F5 and F8 deficiency, factor VII/ FVII/F7 deficiency, factor X/FX/F10 deficiency, factor XI/ FXI /F11 deficiency, factor XIII/FXIII/F13 deficiency. In addition, the references to all retrieved studies were evaluated in order to find potentially relevant reports.

3 | RESULTS

3.1 | Selected studies

In the present research, 361 studies were found in initial search and 89 articles were excluded due to duplication. The abstracts of all remaining papers were carefully assessed, and 251 further articles were excluded due to different reasons including PND of common bleeding
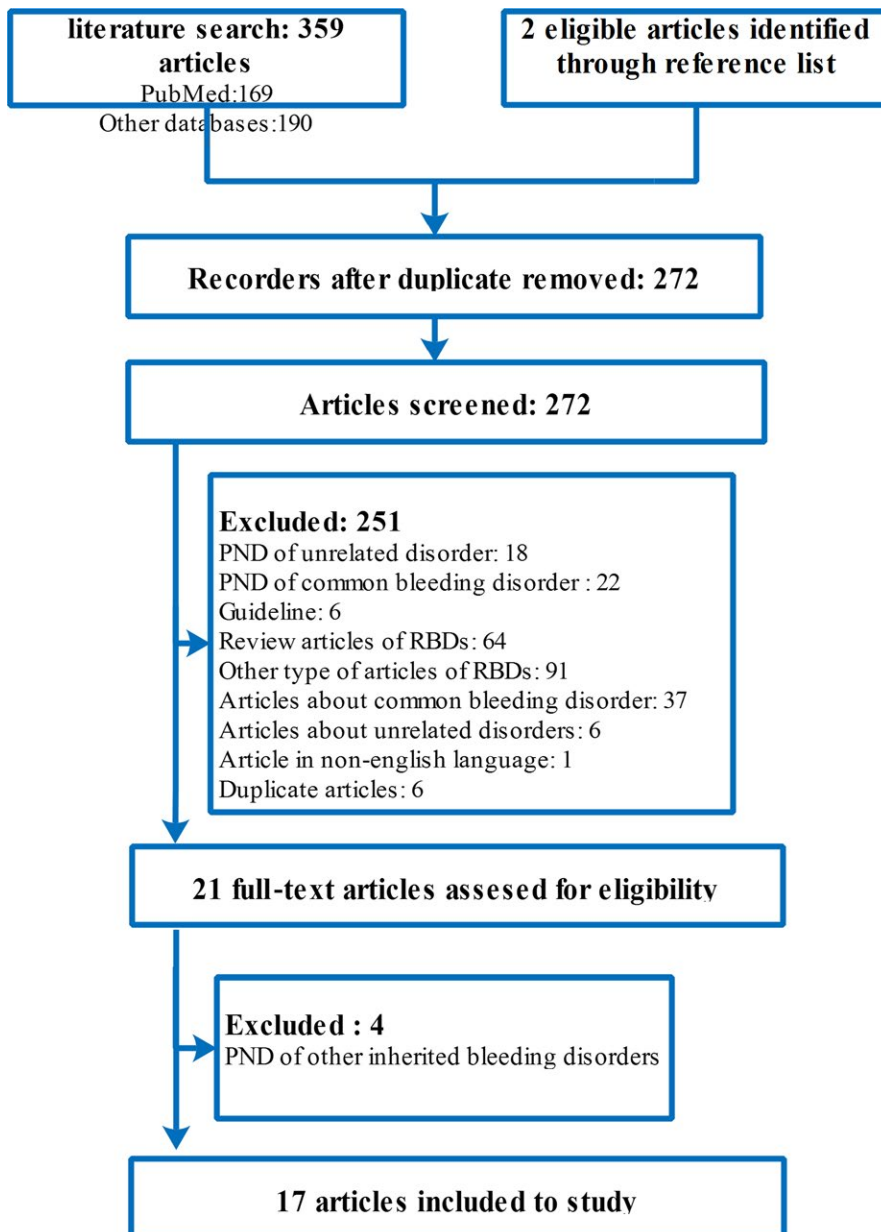
FIGURE 1 Flow chart of systemic review [Colour figure can be viewed at wileyonlinelibrary.com]

disorders, PND of unrelated disorders, review articles, guidelines and non-English articles. By careful screening of all 21 remain studies, 4 more articles about PND of other inherited bleeding disorders were excluded. Finally, by the exclusion of inappropriate papers for this study, 17 studies were selected (Figure 1).

3.2 | Prenatal diagnosis in rare bleeding disorders

In the literature, PND was performed for afibrinogenemia, FVD, FVIID, FXD and FXIIID. A total of 39 PNDs were performed, most commonly for FXIIID (n: 17, 43.6%) and FVIID (n: 12, 30.8%).

For PND, different methods were used including molecular methods (n: 29, 74.4%), factor assay (n: 8, 20.5%) and simultaneous use of both methods (n: 2, 5.1%). More employed methods included direct sequencing (n: 16, 41%), direct sequencing plus linkage analysis (n: 3, 7.7%), direct sequencing plus factor assay (n: 2, 5.1%), factor assay (n: 8, 20.5%), linkage analysis (n: 1, 2.6%), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) plus linkage analysis (n: 1, 2.6%) and PCR-RFLP for a specific mutation (n: 8, 20.5%). Factor assay was used more commonly in FXD (50% of cases with FXD), and only was performed for 3 and 1 patients of FVD and FXIIID, respectively. Linkage analysis, as the only diagnostic test, was performed in 1 case with FXIIID (6.6%). In Iran, a unique mutation was only used to screen FXIIID and all suspected cases using PCR-RFLP technique (p.Trp187Arg, c.559T>C), a relatively similar feature was reported for FVIID in some relatives in Lebanon with c.291+1G>C mutation. In all other cases with direct sequencing, a specific mutation, which was determined by whole exon sequencing of affected gene in foetus's family, was used for PND.

Among 39 foetuses with PND, 7 of them (18%) (homozygotes: 3, compound heterozygotes: 2, very low factor level: 2) had severe factor deficiency, 19 (48.7%) were heterozygotes and 13 (33.3%) were normal. Besides, 6 of foetuses had severe factor deficiency and 3 had congenital FXIIID. In the first case, parents decided to terminate the pregnancy, in the second case, they experienced foetal ICH and baby was born with hydrocephalus, and in the third case, data were not available. All other pregnancies were uneventful except for 1 patient with severe FVIID, who experienced ICH a few days postdelivery. Family history and details for 11 out of 39 cases were not available. All the remaining cases (n: 28) had an underlying congenital bleeding disorder in their family history. The most common presentation led to request a PND was ICH (n: 16, 57.1%). ICH-related death was reported in 6 (21.4%) families, while in 4 (14.2%) cases, the causes of deaths were not specifically determined. The postcircumcision die also was reported in 1 (3.7%) case.

3.3 | Factor I deficiency

The only report of PND in afibrinogenemia was about a Palestinian family with 2 affected children and ICH occurrence after minor trauma. Direct sequencing of FGA and FGG genes failed to detect the underlying mutation, but in the DNA sequencing of FGB, a nonsense mutation (p.Trp467Stop) was identified in homozygotes and

TABLE 1 Prenatal diagnosis of families with congenital fibrinogen deficiency and factor V deficiency

N	Type of deficiency	Author	Year	Time of sampling (week)	Family history	Detection	Mutation	Foetus statue	CB factor activity	Confirmation after birth	References
1	FID	Neerman et al.	2003	16	+	MD	Trp467Stop (TGG>TAG)	Heterozygous	–	+	10
2	FVD	Daffos et al.	1988	22	+	FA	UD	Unaffected	22.5%	+	11
3	FVD	Cao et al.	2011	12	+	MD (DS) /FA	G16088C (p. Gly67Arg)	Heterozygous	15%	+	12
4	FVD	Cao et al.	2011	12	+	MD (DS) /FA	C69969T (p.Gly2079Val)	Unaffected	32%	+	12

N, number; FA, factor assay; MD, molecular detection; DS, direct sequencing; UD, undetermined; CB, cord blood

heterozygote states in affected siblings and parents, respectively. Amniocentesis was performed in the 16th week of gestation, and amniotic fluid cells were cultured and analysed to determine the underlying mutation. In addition to direct mutation detection, microsatellite analysis of the FGA Intron 3 Tetranucleotide Repeat (FGAi3) was performed on the foetus and confirmed heterozygote state of the foetus (Table 1).[10]

3.4 | Factor V deficiency

Until now, only 3 cases of PND were performed for diagnosis of FVD in—foetal period, which 2 foetuses were unaffected and 1 was in the heterozygote state. In the first family, with a history of a child with homozygote FVD, who died due to ICH, PND was performed in next pregnancy and FV activity level of foetal was determined in the 22nd week of gestation and unaffected foetus was reported.[11] In another study, first child of the family was diagnosed with FVD (FV activity: 5%) due to dental postextraction bleeding. The child had no parental consanguinity, and his parents had no bleeding problem. In the second pregnancy, the couple decided to undergo PND. The FV levels of mother and father were 63% and 49%, respectively. The first child was confirmed to be homozygous for G16088C missense mutation (p.Asp68His) in exon 3 of FV gene (F5), and his parents were heterozygous for this mutation. The factor level of the foetus was 15% (normal range at 22 weeks: 21%-44%), and the foetus was also heterozygous for this mutation.[12]

The third family had a history of a child who suffered from severe recurrent nasal haemorrhage required blood transfusion. The FV activity was 2%, and he was born from consanguineous marriage. In the second pregnancy, after consolation, the parents decided to undergo PND. Sequencing was shown the homozygous for C69969T (p.Gly-2079Val) missense mutation. The parents were carrier for this mutation. Mutation analysis and cord blood factor assay were performed on the foetus. The factor activity of foetus was 32%, which was in normal range (normal range at 22 weeks: 21%-44%) and the mutation was not detected in the foetus (Table 1).[12]

3.5 | Factor VII deficiency

In the literature, there are only a few reports on PNDs in congenital FVIID. Almost all reports are about families with a positive family history of FVIID and ICH. In fact, like other RBD, the severity of disorder and history of ICH provoke parents to request a PND. In the first case, a family with congenital FVIID and history of a child with severe FVIID who died due to ICH at 4 months of life were reported. PND was performed in next pregnancy at the 24th week of gestation and FVII activity was 4%. In the 37th week of gestation, prenatal transfusion of FVII concentrate (200 IU) was performed 1 hour before caesarean that increased FVII activity to 100%. In this case, neonate was born with FVII activity of 75% and 6%, just after birth and 7 hours after birth, respectively.[11] The second PND was reported in 1992. Parents were heterozygous for FVIID. They had 1 child with compound heterozygotes for 2 single nucleotide deletions in FVII gene (c.10698del

TABLE 2 Prenatal diagnosis of families with congenital factor VII deficiency

N	Author	Year	Time of sampling (week)	Family history	Detection	Mutation	Foetus statue	CB factor activity	Confirmation after birth	Reference
1	Daffos et al.	1988	24	+	FA	UD	Severe deficiency	4%	+	11
2	Millar et al.	1992	10	+	MD(DS)	-	Unaffected	-	+(FVIIC: 15%)	13
3	Mcvey et al.	1998	10	+	MD (DS)	-	Unaffected	62%	-	14
4	Giansily et al.	2001	14	+	MD (DS/LA)	-	Unaffected	-	-	15
5	Ariffin et al.	2003	10	+	MD (DS)	IVS5-2 A>G	Heterozygote	-	+(FVIIC: 33%)	16
6	Mota et al.	2007	19	+	FA	-	Unaffected	22%	+	17
7	Farah et al.	2007	-	+	MD (DS)	c.291+1G>C	Homozygote	-	+(FVIIC: <2%)	18
8	Farah et al.	2015	-	+	MD(DS-exon 2)	c.291+1G>C	Homozygote	-	+	19
9	Shetty et al.	2007	-	NM	FA	-	Unaffected	+a	+a	20
10	Peng et al.	2016	NA	+	MD (DS)	c.572-1G>A	Heterozygote	NA	NA	21

N, number; NM, non-mentioned; NA, Not available; MD, molecular detection; DS, direct sequencing; FA, factor assay; LA, linkage analysis; CB, cord blood; UD, undetermined.
aFactor level was not mentioned.

TABLE 3 Prenatal diagnosis of families with congenital factor X deficiency

N	Author	Year	Time of Sampling (week)	Family history	Detection	Mutation	Foetus statue	CB factor activity	Confirmation at birth	Reference
1	Camire et al.	2003	11	1	MD (DS)	-	Unaffected	-	+ (FXC: 36%)[a]	22
2	Camire et al.	2003	NM	1	MD (DS+LA)	Tyr279Asn	Heterozygote	-	+ (FXC: 22%)	22
3	Mota et al.	2007	18.5	1	FA	-	Unaffected	21%	+	17
4	Sheety et al.	2007	NM	NM	FA	-	Unaffected	+[a]	+[b]	20
5	Sheety et al.	2007	NM	NM	FA	-	Unaffected	+[a]	+[b]	20
6	Ingerslev et al.	2007	NA	1	MD(DS)	Glu16Lys Val298Met	Double Heterozygote	-	+(FXC:<1%)	7

N, number; NM, non-mentioned; NA, Not available; MD, molecular detection; DS, direct sequencing; FA, factor assay; LA, linkage analysis; CB, cord blood; UD, undetermined.

[a] The assay at 10th day of life.

[b] The factor level was not mentioned.

C and c.10785del C) that experienced ICH 2 times and once GI bleeding; therefore, chorionic villus sampling was taken in the 10th week of gestation. The existence of 2 parental wild-type alleles indicated normal phenotype in PND study.[13] Mcvey et al assessed parents with consanguinity and history of died girl due to cerebral haemorrhage and hydrocephaly. Both parents were heterozygote for FVIID. Therefore, PND was performed in next pregnancy and the boy was nonmutant for FVII gene mutation (IVS4+1G>A).[14] In another study, FVII direct gene mutation detection and linkage analysis were used for PND and the unaffected foetus was reported.[15] Ariffin et al reported a foetus with carrier parents for FVIID. They also had a history of 2 died children with FVIID and massive ICH. PND study indicated heterozygote states of a foetus that was born with normal delivery without any complication.[16] Mota et al, studied a family with FVIID and history of 2 died children with FVIID due to cerebral haemorrhage at age of 5 weeks and 13 months, respectively. PND showed that the foetus was unaffected.[17] Farah et al reported a 1-month age girl with FVIID who diagnosed with PND. The girl was received recombinant FVII as secondary prophylaxis after the occurrence of CNS bleeding. The girl was homozygote for c.291+1G>C mutation. Her parents were consanguineous, and their child was born full term without any complication. Eight years later, in another study, Farah et al reported another PND analysis in which c.291+1G>C was used as a screening marker in 2 close relative families.[18,19] Shetty et al conducted a comprehensive study on a large number of families (n: 172) with haemophilia and RBD and an unaffected foetus in a family with FVIID was identified.[20] The last report was performed by Peng et al. They assessed FVII underlying gene mutation in proband and parents. Proband was homozygous for FVII c.572-1G>A gene mutation and parents and foetus were heterozygote (Table 2).[21]

3.6 | Factor X deficiency

Only in 6 cases, PND has been used in FXD up to now, which 4 had a positive family history of FXD and the data of 2 families were not available. The first family had a child with prolonged postcircumcision bleeding, which managed with administration of fresh frozen plasma (FFP). Moreover, the child was also suffered from the intracerebral bleed. Laboratory assessments revealed that FX level was less than 1%. Mutational analysis of proband and parents revealed that the proband inherited the loss of function mutation of his father. Despite the whole FX exon sequencing, no mutation was found in the mother. In the second pregnancy, the couple decided to undergo PND. The mutation analysis revealed that foetus did not inherit the mutation of the father but there was still 50% chance of being a carrier of FXD due to mother's undetectable mutation. The foetus was born without complication, and the FX level was 36%. At age of 2 years, the FX level was 65%, which demonstrated the presence of a maternal mutation and heterozygote status in the child. At third pregnancy, the couple again decided to request PND. Mutational analysis revealed that the foetus inherited paternal mutation and there was a 50% chance of being homozygous for FXD. As maternal mutation was undetectable, linkage analysis was performed and it was shown that the foetus

TABLE 4 Prenatal diagnosis of families with congenital factor XIII deficiency

N	Author	Year	Time of sampling(week)	Family history	Detection	Mutation	Foetus statue	Factor activity (%)	Confirmation after birth	Reference
1	Kangsadalampai et al.	1996	12	+	MD(STR+ PCR-RFLP)	p.Gln400X (1201C>T)	Heterozygote	NO	NM	24
2	Daffos et al.	1998	10	NA	FA	No	Severe deficiency	<5%	No[a]	11
3	Killick et al.	1999	T1	+	MD (DS)	No	Unaffected	94%	+	25
4	Xu et al.	2015	NA	+	MD (DS)	(p.Arg662* & p.Trp665*)	Double heterozygotes	NO	NM	27
5	Naderi et al.	2015	13	+	MD (PCR-RFLP)	p.Trp187Arg (c.559T>C)	Unaffected	<1%	+	23
6	Naderi et al.	2015	12	+	MD (PCR-RFLP)	p.Trp187Arg (c.559T>C)	Heterozygote	<1%	+	23
7	Naderi et al.	2015	14	+	MD (PCR-RFLP)	p.Trp187Arg (c.559T>C)	Heterozygote	<1%	+	23
8	Naderi et al.	2015		+	MD (PCR-RFLP)	p.Trp187Arg (c.559T>C)	Homozygote	<1%	+	23
9	Naderi et al.	2015	T1	+	MD (PCR-RFLP)	p.Trp187Arg (c.559T>C)	Heterozygote	<1%	+	23
10	Naderi et al.	2015	T1	+	MD (PCR-RFLP)	p.Trp187Arg (c.559T>C)	Heterozygote	<1%	+	23
11	Naderi et al.	2015	T1	+	MD (PCR-RFLP)	p.Trp187Arg (c.559T>C)	Heterozygote	<1%	+	23
12	Naderi et al.	2015	T1	+	MD (PCR-RFLP)	p.Trp187Arg (c.559T>C)	Heterozygote	<1%	+	23
13	Shanbhag et al.	2016	T1	+	MD (DS)	-	Unaffected	No	+[b]	26
14	Shanbhag et al.	2016	T1	+	MD (DS)	p.Ser19Pro (c.58T>C)	Heterozygote	No	+[b]	26
15	Shanbhag et al.	2016	T1	+	MD (DS)	Deletion of exon 3	Heterozygote or normal	No	+[b]	26
16	Shanbhag et al.	2016	T1	+	MD (DS)	p.Trp130X (c.392G>A)	Heterozygote	No	+[b]	26
17	Shanbhag et al	2016	T1	+	MD (DS)	p.Arg244X (c.733A>T)	Heterozygote	No	+[b]	26

N, number; NM, non-mentioned; NA, Not available; MD, molecular detection, DS, direct sequencing; FA, factor assay; LA, linkage analysis; CB, cord blood; UD, undetermined; T1, first trimester.

[a]Terminate pregnancy.

[b]The factor level was not mentioned.

inherited the normal FX allele of the mother. Therefore, the foetus was heterozygote of FXD.[22]

The third family had a history of a child with severe FXD who experienced haemarthrosis. On the second pregnancy, they requested a PND. Accordingly, the foetal blood sample was taken and the FX level of the foetus was 21% (normal range at 18-20 week of gestation: 10.8%-17.6%), which was unaffected.[17] Sheety et al[20] used factor assay for PND, and 2 unaffected foetuses were diagnosed.

The sixth family had a history of a child with haemarthrosis, muscle bleeding and several mucosal bleeds, which was diagnosed at 17-month age. He was affected by the severe type of FXD. The second child was diagnosed with severe FXD in utero and coagulation studies in neonatal period. At age of 18 months, she was suffered from recurrent mucosal and joint bleeding which managed by FFP. The mutational analysis showed that both children were double heterozygote (p.Glu16Lys and p.Val298Met) (Table 3).[7]

3.7 | Factor XIII deficiency

Prenatal diagnosis most commonly was used for FXIIID. In southeast Iran, p.Trp187Arg mutation in exon 4, routinely was used for PND. Among 8 reported cases from this area, 1 was homozygotes that CT scan revealed intrauterine ICH and neonatal hydrocephalus. Although the mother underwent normal vaginal delivery, a neonate with hydrocephaly was born. Among these families, 3 of 8 had a history of CNS bleeding and 4 (50%) had a positive history of death due to congenital FXIIID.[23] Short tandem repeat (STR) successfully was used in 2 studies for PND.[24,25] Only in 1 case, FXIII assay was performed for PND, which FXIII level was below 5%. Therefore, parents decided to terminate the pregnancy.[11] In a recent study, which was performed on Indian families, PND was conducted for 5 families, and 5 different mutations in FXIII-A gene were detected (Table 4).[26]

4 | DISCUSSION

Intracranial haemorrhage is the most dreadful complication and the main cause of death among patients with RBD. This life-threatening diathesis has 2 main consequences including death or neurological complications.[4] ICH and related morbidity and mortality are the main causes to request a PND for subsequent pregnancy.[10] But other severe bleeds are also led to undergo a PND. Due to the high rate of spontaneous ICH in congenital FXIIID, PND can be requested for any foetus suspected to severe congenital FXIIID. It is routinely performed in southeast Iran that presents the high rate of disorder.[23] The frequency of ICH is ranged from 0% for FXID to ~30% for FXIIID. PND was requested for those families with previous history of ICH. For FVD, even recurrent nasal bleeding led to a PND request. Although PND is useful in RBD, several issues should be considered before performing. Accordingly, the healthcare services, which include a team of obstetrician, haematologist, paediatrician and clinical genetics expertise, provide multidisciplinary care for mothers and foetus. The aim of this service is to provide different aspects of obstetric management including preconceptual counselling, PND and post-PND cares.[28] Preconceptual counselling, which should be precede PND, is the critical step that provides the information about the option of PND by considering the limitations and potential complications and also the bleeding risks to mother and foetus.[28,29] The main advantage of PND is to minimize or prevent the life-threatening bleeds.[2] In one of affected foetus with FXIIID, intrauterine ICH occurred and a foetus with hydrocephalus was born. Although foetal ICH is rare, it has been reported in congenital FVD, FVIID and FXD as well as classical haemophilia.[7,9] Therefore, for mothers with affected foetus and high risk of life-threatening bleeding, post-PND precautions should be considered.[8] An important issue is that an affected foetus with high risk of life-threatening bleeding during pregnancy or labour has indication of intrauterine factor transfusion. This was performed for a foetus with severe FVIID, just before labour and delivery occurred without any abnormal bleeding.[11] Although this case had good outcome, several foetuses with severe FVIID were delivered without such intervention.[1] But it should be considered that ICH during labour is a challenge in patients with high risk of ICH such as congenital FXIIID.[2] Type of delivery is another crucial issue. This issue is investigated more frequently in classical haemophilia and as a result, uncomplicated normal vaginal delivery is a better option.[2,30,31] Generally, the rate of ICH in delivery with forceps, vacuum extraction, caesarian section during labour and caesarian section before labour are 1 per 664, 860, 907 and 2750, respectively.[2,30,32] Based on the available experiences for PND in congenital bleeding disorders, even vaginal delivery lead to the occurrence of ICH in congenital FXIIID and a considerable number of these patients experience this diathesis during labour.[1,2,23] Therefore, further studies are required to resolve this issue. Another very important question is about postdelivery precautions. Although except in severe congenital FXIIID, there is no consensus about primary prophylaxis in other RBD, it is recommended that patients with other RBD such as FXD, FVIID and afibrinogenemia with severe life-threatening bleeds consider the secondary prophylaxis. But sometimes lack of primary prophylaxis in these patients leads to fatal consequences; therefore, some experts consider primary prophylaxis for their high-risk patients.[18,19] Even in cases with successful delivery subsequent to PND, life-threatening ICH occurred in the first days of life.[2,4,18,19]

Generally, PND is conducted in the first and the second trimesters via testing of placental or amniotic fluid samples. These invasive methods have 1% risk of miscarriage and provide an option of terminating the pregnancy in the women with the affected foetus. However, it is the rationale that women who prefer to continue their pregnancies be aware of the mutation status[33] and delivery of an affected baby should take special consideration. Recently, PND is suggested in third-trimester amniocentesis (after 34 weeks of gestation) as an option to avoid the miscarriage, which results from early testing.[28,33] Some studies suggested the late amniocentesis was a safe technique.[33] However, because there is limited practical experience in PND of RBD, no established data are available for the safety and acceptability of third trimester PND. In addition, third-trimester amniocentesis has about 1% complications related to the procedure

TABLE 5 Coagulation factor activity (%) of foetus and newborn

Factors activity level	Gestation age (weeks)			
	19-23	24-29	30-38	Newborns
FI (g/L, Clauses)	0.85 (0.57-1.50)	1.12 (0.65-1.65)	1.35 (1.25-1.65)	1.68 (0.95-2.45)
FII	16.9 (10-24)	19.9 (11-30)	27.9 (15-50)	43.5 (27-64)
FV	32.1 (21-44)	36.8 (25-50)	48.9 (23-70)	89.9 (50-140)
FVII	27.4 (17-37)	33.8 (18-48)	45.9 (31-62)	52.5 (28-78)
FX	20.5 (14-29)	24.9 (16-35)	28.0 (16-36)	39.6 (21-65)
FXI	13.2 (8-19)	12.1 (6-22)	14.8 (6-26)	37.2 (13-62)

FI, factor I.

Values are reported as mean, followed by parenthesis including lower and upper boundaries of 95% of the population.

including preterm delivery, rupture of membrane and infections. Moreover, there is a probability of failing to obtain a sample (about of 1%) and unexpected delivery before the PND, which result in further stress for the families and their foetus.[28,34] Therefore, the decision about the time of PND should be made based on potential benefits, the risk of procedures, the mother statue and opinion of expertise.[28]

Although direct sequencing is the most common method for PND, it should be considered that due to the heterogeneous nature of mutations and the large size, and complexity of some coagulation factors genes, direct sequencing was not able to detect all mutations. In ~5% patients with RBD, the underlying mutation is not detectable, but new technologies such as next-generation sequencing (NGS) can improve this situation.[1,5] In the present research, 1 of 39 cases, underlying FX gene mutation, was not detectable and linkage analysis was applied as an alternative method.[22] Due to insufficient and limited resources in developing countries and costly determination of direct mutation detection, this method is not practical. Indirect detection (linkage analysis) using informative polymorphic markers is an auxiliary technique for PND of RBD in developing countries.[35] By considering the limitations of linkage analysis, the rate of misdiagnosis should be decreased. One of the limitations is to undergo the study of entire family of the patients for PND. The most serious problem with the linkage analysis is the possibility of recombination between linked markers and disease locus that can lead to misdiagnosis. To overcome this problem, the use of at least 1 proximal and 1 distal flanking marker is suggested. Although this can minimize the risk of incorrect diagnosis, it is not applicable for all cases. Moreover, as the selection of informative markers may be time-consuming, it is better to select the markers before prenatal sampling.[22] Preimplantation genetic diagnosis (PGD) is another technique, which can be used instead of PND. PGD uses the in vitro fertilization (IVF) to create and test each embryo to find the genetic defects related to RBD and consequently identify the unaffected embryo to transfer to utero.[36] PGD is indicated in families who avoid using invasive methods and in countries, which pregnancy termination is not acceptable. However, this method is still challenging and has different limiting factors.[28,36]

Cordocentesis, which perform to determine the cord blood factor level from 18 weeks of gestation, is rarely used today. This method is used in countries, which genetic analysis is not available or in the situations that genetic testing does not give an informative result.[29] In about one-fifth of cases, selected test for PND was factor assay, but whenever reliable molecular methods including direct sequencing are available, such assays are not recommended. In the cases that factor assay is used as a diagnostic test for PND, all the limitations should be considered. For such studies, the purity of foetal sample plays an important role and a diluted sample can affect the results of coagulation assays. To overcome this problem, several simple ways can be used. The first recommendation is that the foetus blood samples should be collected in smaller volumes in several separated aliquots, and the proportion of citrate sodium anticoagulant to blood sample should be kept constant. This can prevent dilution of foetus blood with anticoagulant or amniotic fluid. It is observed that in the first tube, the level of a factor is false while in subsequent small samples of aliquots this problem is resolved. Another recommendation is multiple factor assays that use other coagulation factors as an indicator to find any contamination with maternal fluids.[20] Another problem is that the coagulation system is not well developed in the parental period; therefore, the activity level of most of the coagulation factors is lower in this period compared with adults. In addition, due to the difficulties in the foetal blood samples obtaining, a few studies report the reference range for coagulation factor activity in the parental period. However, knowing about the reference range of coagulation factors in the foetus is necessary to avoid the misdiagnoses (Table 5).[37]

Due to limited available studies and cases as a major limitation of the present study, it was challenging to propose the precise guideline. However, several important points should be considered in performing a PND. First, it should be considered that not all patients with RBD have an indication for PND. PND can be used for all patients with severe congenital FXIIID and for those other RBD with severe factor deficiency and history of life-threatening bleeds,[23] because performing such an invasive procedure with a risk of foetal loss, should offer more benefits than dangers. Moreover, limitations of available diagnostic tests should be considered. In the high-risk foetus, appropriate precautions also should be considered, during pregnancy, within labour and postdelivery,

to choose an appropriate therapeutic regimen. By regarding these issues, PND can be a lifesaving procedure for high-risk families.

ORCID

A. Dorgalaleh http://orcid.org/0000-0002-0125-9319

REFERENCES

1. Dorgalaleh A, Alavi SER, Tabibian S, et al. Diagnosis, clinical manifestations and management of rare bleeding disorders in Iran. *Hematology*. 2016;22:1-7.
2. Rafiee SE, Jalalvand M, Assadollahi V, Tabibian Sh, Dorgalaleh A. Intracranial hemorrhage: a devastating outcome of congenital bleeding disorders- prevalence, diagnosis and management, with a special focous on congenital factor XIII deficiency. *Semin Thrombo Hemost*. 2018;44:267-275.
3. Mumford AD, Ackroyd S, Alikhan R, et al. Guideline for the diagnosis and management of the rare coagulation disorders. *Br J Haematol*. 2014;167:304-326.
4. 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;95:451-455.
5. Palla R, Peyvandi F, Shapiro AD. Rare bleeding disorders: diagnosis and treatment. *Blood*. 2015;125:2052-2061.
6. Naderi M, Dorgalaleh A, Alizadeh S, 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;100:443-449.
7. Ingerslev J, Herlin T, Sorensen B, Clausen N, Chu KC, High KA. Severe factor X deficiency in a pair of siblings: clinical presentation, phenotypic and genotypic features, prenatal diagnosis and treatment. *Haemophilia*. 2007;13:334-336.
8. Landau D, Rosenberg N, Zivelin A, Staretz-Chacham O, Kapelushnik J. Familial factor VII deficiency with foetal and neonatal fatal cerebral haemorrhage associated with homozygosis to Gly180Arg mutation. *Haemophilia*. 2009;15:774-778.
9. de Sousa C, Clark T, Bradshaw A. Antenatally diagnosed subdural haemorrhage in congenital factor X deficiency. *Arch Dis Child*. 1988;63:1168-1170.
10. Neerman-Arbez M, Vu D, Abu-Libdeh B, Bouchardy I, Morris MA. Prenatal diagnosis for congenital afibrinogenemia caused by a novel nonsense mutation in the FGB gene in a Palestinian family. *Blood*. 2003;101:3492-3494.
11. Daffos F, Forestier F, Kaplan C, Cox W. Prenatal diagnosis and management of bleeding disorders with fetal blood sampling. *Am J Obstet Gynecol*. 1988;158:939-946.
12. Cao L, Wang Z, Li H, et al. Gene analysis and prenatal diagnosis for two families of congenital factor V deficiency. *Haemophilia*. 2011;17:65-69.
13. Millar D, Cooper D, Kakkar V, Schwartz M, Scheibel E. Prenatal exclusion of severe factor VII deficiency by DNA sequencing. *Lancet*. 1992;339:1359.
14. McVey JH, Boswell EJ, Takamiya O, et al. Exclusion of the first EGF domain of factor VII by a splice site mutation causes lethal factor VII deficiency. *Blood*. 1998;92:920-926.
15. Giansily-Blaizot M, Aguilar-Martinez P, Mazurier C, et al. Prenatal diagnosis of severe factor VII deficiency using mutation detection and linkage analysis. *Br J Haematol*. 2001;112:251-252.
16. Ariffin H, Millar DS, Cooper DN, Chow T, Lin H-P. Prenatal exclusion of severe factor VII deficiency. *J Pediatr Hematol Oncol*. 2003;25:418-420.

17. Mota L, Ghosh K, Shetty S. Second trimester antenatal diagnosis in rare coagulation factor deficiencies. *J Pediatr Hematol Oncol*. 2007;29:137-139.
18. Farah RA, Hamod D, Melick N, Giansily-Blaizot M, Sallah S. Successful prophylaxis against intracranial hemorrhage using weekly administration of activated recombinant factor VII in a newborn with severe factor VII deficiency. *J Thromb Haemost*. 2007;5:433-434.
19. Farah R, Al Danaf J, Braiteh N, et al. Life-threatening bleeding in factor VII deficiency: the role of prenatal diagnosis and primary prophylaxis. *Br J Haematol*. 2015;168:452-455.
20. Shetty S, Ghosh K. Robustness of factor assays following cordocentesis in the prenatal diagnosis of haemophilia and other bleeding disorders. *Haemophilia*. 2007;13:172-177.
21. Peng W, Zhang S, Liu X, Gu Y, Wang Y. Mutation analysis and prenatal diagnosis for a family affected with congenital factor VII deficiency. *Chin J Med Genet*. 2016;33:357-360.
22. Camire R, Ann Denchy R, Day GA, Lanzano P, Sheth S, Brown S. Prenatal diagnosis of factor X deficiency using a combination of direct mutation detection and linkage analysis with an intragenic single nucleotide polymorphism. *Prenat Diagn*. 2003;23:457-460.
23. Naderi M, Reykande SE, Dorgalaleh A, 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;27:97-100.
24. Kangsadalampai S, Coggan M, Caglayan SH, Aktuglu G, Board PG. Application of HUMF13A01 (AAAG)n STR polymorphism to the genetic diagnosis of coagulation factor XIII deficiency. *Thromb Haemost*. 1996;76:879-882.
25. Killick CJ, Barton CJ, Aslam S, Standen G. Prenatal diagnosis in factor XIII-A deficiency. *Arch Dis Child Fetal Neonatal Ed*. 1999;80:F238-F239.
26. Shanbhag S, Ghosh K, Shetty S. First trimester prenatal diagnosis of severe FXIII deficiency. *Haemophilia*. 2016;22:e443-e444.
27. Xu G, Liang Q, Zhang L, et al. [Identification of genetic defects in a Chinese pedigree with factor XIII deficiency: case report and literature review]. *Zhonghua xue ye xue za zhi =Zhonghua xueyexue zazhi*. 2015;36:844-848.
28. Kadir R, Davies J, Winikoff R, et al. Pregnancy complications and obstetric care in women with inherited bleeding disorders. *Haemophilia*. 2013;19:1-10.
29. Lee C, Chi C, Pavord S, et al. The obstetric and gynaecological management of women with inherited bleeding disorders–review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization. *Haemophilia*. 2006;12:301-336.
30. Singleton TC, Keane M. Diagnostic and therapeutic challenges of intracranial hemorrhage in neonates with congenital hemophilia: a case report and review. *Ochsner J*. 2012;12:249-253.
31. Vacca A. Effect of mode of delivery on neonatal intracranial injury. *N Engl J Med*. 2000;342:893.
32. Kulkarni R, Ponder KP, James AH, et al. Unresolved issues in diagnosis and management of inherited bleeding disorders in the perinatal period: a White Paper of the Perinatal Task Force of the Medical and Scientific Advisory Council of the National Hemophilia Foundation, USA. *Haemophilia*. 2006;12:205-211.
33. Cutler J, Chappell L, Kyle P, Madan B. Third trimester amniocentesis for diagnosis of inherited bleeding disorders prior to delivery. *Haemophilia*. 2013;19:904-907.
34. Huq F, Kadir R. Management of pregnancy, labour and delivery in women with inherited bleeding disorders. *Haemophilia*. 2011;17:20-30.
35. Peyvandi F, Jayandharan G, Chandy M, et al. Genetic diagnosis of haemophilia and other inherited bleeding disorders. *Haemophilia*. 2006;12:82-89.

36. Peyvandi F, Palla R, Menegatti M, Mannucci PM, editors. Introduction: rare bleeding disorders: general aspects of clinical features, diagnosis, and management. *Semin Thromb Hemost*. 2009;35:349-355. © Thieme Medical Publishers.

37. Reverdiau-Moalic P, Delahousse B, Body G, Bardos P, Leroy J, Gruel Y. Evolution of blood coagulation activators and inhibitors in the healthy human fetus. *Blood*. 1996;88:900-906.