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Case Report

Isolated Severe Prolongation of Prothrombin Time Revealing Congenital Factor VII Deficiency With Mild Bleeding Phenotype: A Case Report

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ABSTRACT

Congenital Factor VII (FVII) deficiency is a rare inherited bleeding disorder characterized by marked variability in bleeding severity and poor correlation between factor activity levels and clinical phenotype. We report a 21-year-old woman who presented with recurrent spontaneous ecchymoses without mucosal bleeding, menorrhagia, hemarthrosis, or prior excessive surgical bleeding. Laboratory evaluation demonstrated markedly prolonged prothrombin time (PT) of 96 seconds with an international normalized ratio (INR) of 8.0 and normal activated partial thromboplastin time (aPTT). Repeat testing confirmed persistent isolated PT prolongation. There was no evidence of liver disease, vitamin K deficiency, anticoagulant exposure, disseminated intravascular coagulation, systemic illness, or malignancy. A PT mixing study completely corrected the abnormal PT, supporting a factor deficiency rather than an inhibitor. Specific factor assays demonstrated isolated severe FVII deficiency with activity <5.6%, while Factors II, IX, and X were normal. Despite severe laboratory abnormalities, the patient had only mild cutaneous bleeding manifestations and had previously undergone uneventful septorhinoplasty. She was managed conservatively with education and individualized follow-up. This case highlights the important discordance between PT/INR severity and bleeding phenotype in congenital FVII deficiency. This case highlights extreme PT/INR prolongation with severe FVII deficiency but mild phenotype and prior uneventful surgery, emphasizing that INR should not be interpreted like warfarin-associated coagulopathy in congenital FVII deficiency.

Key words: Factor VII deficiency, isolated prolonged prothrombin time, INR, coagulation disorder, mild bleeding phenotype, case report

INTRODUCTION

Disorders of hemostasis may present as life-threatening hemorrhage, mild mucocutaneous bleeding, or incidental abnormalities on coagulation testing. Isolated prolongation of prothrombin time (PT) with a normal activated partial thromboplastin time (aPTT) localizes the abnormality to the extrinsic pathway. The differential diagnosis includes vitamin K deficiency, early or subclinical liver disease, vitamin K antagonist exposure, and FVII deficiency. [1] FVII is a vitamin K-dependent serine protease synthesized in the liver; after binding tissue factor, it initiates thrombin generation and fibrin formation through activation of downstream coagulation factors. [2]

Congenital FVII deficiency is among the most frequent rare autosomal recessive bleeding disorders, with an estimated prevalence of approximately 1 in 300,000 to 1 in 500,000 individuals, though prevalence may be higher in consanguineous populations. [3,4] Its clinical phenotype is highly heterogeneous, ranging from asymptomatic laboratory abnormalities to severe intracranial hemorrhage, gastrointestinal bleeding, hemarthrosis, or perioperative bleeding. [5,6] Unlike hemophilia A and B, FVII deficiency shows a weak relationship between factor activity level and bleeding phenotype. [5,7]

We hereby present a case of a 21-year-old woman with markedly prolonged PT/international normalized ratio (INR; 96 seconds/8.0) and severe isolated FVII deficiency (<5.6%) who presented with only mild spontaneous ecchymoses and had previously undergone septorhinoplasty without excessive bleeding. This case emphasizes the significant discrepancy between laboratory severity and clinical presentation in congenital FVII deficiency and points out the necessity for personalized management that considers bleeding history and procedural risk instead of relying solely on PT/INR values.

CASE REPORT

A 21-year-old previously healthy woman presented to the hematology clinic with recurrent spontaneous ecchymoses and bruising involving the upper and lower extremities, abdomen, and back. The bruises occurred spontaneously without preceding trauma. She denied fever, weight loss, fatigue, epistaxis, gingival bleeding, hematuria, gastrointestinal bleeding, menorrhagia, joint swelling, hemarthrosis, or deep tissue bleeding. She also reported no excessive bleeding after septorhinoplasty performed two years earlier, dental procedures, minor cuts, or vaccinations.

Her past medical history was unremarkable. She was not taking regular medications and reported no exposure to anticoagulants, antiplatelet agents, or herbal supplements. There was no history of prolonged or recent antibiotic use, malnutrition, fat malabsorption, cholestatic disease, or liver disease. She reported an allergy to Augmentin. Family history was notable for a grandmother with a possible but unspecified congenital bleeding disorder. She was a university student, a non-smoker, and did not consume alcohol. Her menstrual cycles were regular without menorrhagia. A formal ISTH bleeding assessment score was not recorded at the index visit.

On examination, she was alert, oriented, and hemodynamically stable. Multiple diffuse, non-palpable ecchymoses were present over the limbs, abdomen, and back. There were no petechiae, palpable purpura, mucosal lesions, or signs of active bleeding. There was no pallor, lymphadenopathy, hepatosplenomegaly, or joint swelling. Cardiovascular, respiratory, abdominal, neurological, and musculoskeletal examinations were otherwise unremarkable.

Initial laboratory investigations are summarized in **Table 1**. Complete blood count, platelet count, renal profile, liver biochemical tests, albumin, thyroid profile, and iron studies were within reference ranges. Coagulation testing showed a markedly prolonged PT of 96 seconds (INR, 8.0) with an aPTT of 28 seconds, which was within normal limits for our laboratory. The abnormal coagulation profile was repeated on a newly collected sample, showing PT 94 seconds (INR, 7.9) and aPTT 29 seconds, reducing the likelihood of pre-analytical error. The thromboplastin reagent and International Sensitivity Index (ISI) were not available in the clinical dataset used for this report; therefore, reagent sensitivity may have contributed to the numerical extremity of the PT/INR, but repeat testing and subsequent factor assays confirmed a true isolated extrinsic-pathway factor deficiency.

In evaluating the isolated PT prolongation, acquired causes were actively considered. There was no clinical or laboratory evidence suggestive of vitamin K deficiency, liver dysfunction, acute inflammatory or septic illness, malignancy, disseminated intravascular coagulation, or anticoagulant exposure. Normal activities of other vitamin K-dependent factors (Factor II, IX, and X) further argued against vitamin K deficiency or a global defect in vitamin K-dependent factor synthesis and supported isolated FVII deficiency.

A PT mixing study was performed to distinguish factor deficiency from a circulating inhibitor. Patient plasma was mixed 1:1 with normal pooled plasma, and PT corrected from 96 seconds to 13.2 seconds (reference range 11–13.5 seconds), supporting factor deficiency rather than an inhibitor.

Table 1: Baseline hematologic and biochemical parameters at presentation.

Parameter	Patient value	Reference range	Interpretation
Hemoglobin	13 g/dL	12.0–15.5 g/dL	Normal
White blood cell count	5 × 10^9/L	4.0–11.0 × 10^9/L	Normal
Platelet count	335 × 10^9/L	150–450 × 10^9/L	Normal
PT	96 s	11–13.5 s	Markedly prolonged
INR	8.0	0.9–1.2	Markedly prolonged
aPTT	28 s	25–35 s	Normal for the laboratory
Total bilirubin	0.6 mg/dL	0.2–1.2 mg/dL	Normal
ALT	22 U/L	10–40 U/L	Normal
AST	24 U/L	10–40 U/L	Normal
Alkaline phosphatase	70 U/L	30–120 U/L	Normal
Albumin	4.2 g/dL	3.5–5.0 g/dL	Normal synthetic marker
Creatinine	0.8 mg/dL	0.6–1.2 mg/dL	Normal
Blood urea nitrogen	12 mg/dL	7–20 mg/dL	Normal
TSH	1.8 mIU/L	0.4–4.0 mIU/L	Normal
Serum iron	85 µg/dL	50–170 µg/dL	Normal
Ferritin	45 ng/mL	15–150 ng/mL	Normal
Total iron-binding capacity	320 µg/dL	250–450 µg/dL	Normal

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time; TSH, thyroid-stimulating hormone.

Specific coagulation factor assays then demonstrated severely reduced FVII activity reported as <5.6% (reference range 50%–150%; lower reportable limit in the laboratory report), while Factor II was 92% (70%–120%), Factor IX was 88% (60%–140%), and Factor X was 95% (70%–150%). These results confirmed isolated severe FVII deficiency.

Given the absence of active bleeding, severe mucosal bleeding, hemarthrosis, intracranial bleeding, gastrointestinal bleeding, or high-risk clinical features, she was managed conservatively with clinical observation and individualized follow-up. She was educated to avoid non-steroidal anti-inflammatory drugs, antiplatelet agents, and unnecessary intramuscular injections; to inform healthcare providers of her diagnosis before procedures; and to seek urgent care for mucosal, gastrointestinal, post-traumatic, or persistent bleeding. Family screening with PT and FVII activity testing was recommended for first-degree relatives, and genetic counselling was discussed because congenital FVII deficiency is autosomal recessive and has implications for reproductive planning.

DISCUSSION

Diagnostic Approach to Isolated Prolongation of Prothrombin Time

This case demonstrates a practical approach to isolated PT prolongation in an otherwise healthy young woman. The first step was confirmation on a newly collected sample, because sampling error, under-filled citrate tubes, clotting in the sample, or laboratory artifact can produce misleading coagulation results. Persistent PT prolongation with a normal aPTT localized the abnormality to the extrinsic pathway. Medication review and clinical evaluation did not identify vitamin K antagonist exposure, liver disease, vitamin K deficiency, systemic inflammatory illness, sepsis, malignancy, or consumptive coagulopathy. In addition, normal Factors II, IX, and X strongly argued against vitamin K deficiency or generalized impaired synthesis of vitamin K-dependent factors. [1] The diagnostic algorithm applied to isolated prolonged PT with normal aPTT is summarized in **Figure 1**.

Distinguishing Congenital From Acquired FVII Deficiency

Acquired isolated FVII deficiency is uncommon but should be considered before confirming congenital disease. Reported mechanisms include autoantibodies against FVII, severe systemic illness, malignancy, liver dysfunction, and consumptive states. In this patient, the complete correction of PT in the mixing study supported factor deficiency rather than an inhibitor, and the absence of systemic illness or malignancy made an acquired consumptive process less likely. [8] The patient's young age, family history of a possible bleeding disorder, isolated severe reduction in FVII activity, and normal levels of other vitamin K-dependent factors collectively favored congenital isolated FVII deficiency. The principal

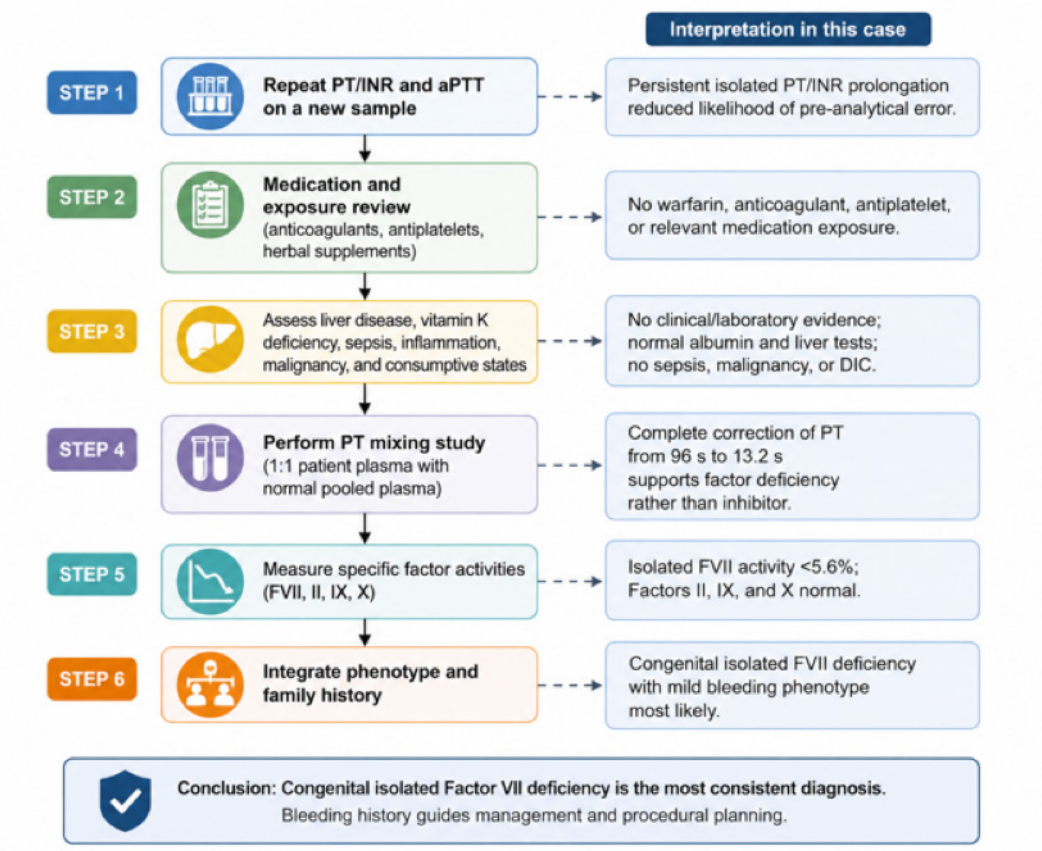

Figure 1: Diagnostic algorithm applied to isolated prolonged prothrombin time (PT) with normal activated partial thromboplastin time (aPTT). The figure illustrates the sequential evaluation of persistent isolated PT prolongation, including repeat testing, exclusion of acquired causes, PT mixing study interpretation, and specific coagulation factor assays leading to the diagnosis of congenital isolated Factor VII (FVII) deficiency.

differential diagnoses considered in the evaluation of isolated prolonged PT with normal aPTT are summarized in **Table 2**.

This table summarizes major differential diagnoses for isolated prolonged PT with normal aPTT and highlights distinguishing laboratory and clinical features relevant to diagnostic evaluation.

Discordance Between Severe Laboratory Abnormality and Mild Clinical Phenotype

The most striking feature is the discordance between severe laboratory abnormality and mild clinical phenotype. Although FVII activity below 10% is often considered severe, bleeding risk in congenital FVII deficiency is not predicted reliably by factor activity alone. [5,7] Large registry data have shown wide phenotypic variation, including asymptomatic or mildly symptomatic patients despite very low FVII levels. [4,9] This patient had only cutaneous ecchymoses and no menorrhagia, mucosal bleeding, hemarthrosis, gastrointestinal bleeding, intracranial bleeding, or excessive bleeding after septorhinoplasty. Her prior nasal surgery is particularly informative because it represents a meaningful hemostatic challenge in a vascular mucosal site.

Interpretation of Extreme INR in Congenital FVII Deficiency

The INR value of 8.0 is clinically striking and may be alarming if interpreted as equivalent to warfarin-associated coagulopathy. However, INR calibration was developed primarily to standardize PT for monitoring vitamin K antagonist therapy. In congenital FVII deficiency, INR may not reflect bleeding risk in the same manner, because the defect is isolated and the clinical phenotype depends on multiple factors beyond the PT/INR value, including mutation type, residual protein function, tissue factor pathway biology, and personal bleeding history. [5,10] Furthermore, PT can vary depending on thromboplastin reagent sensitivity. Because the reagent and ISI were not available from the clinical dataset, this limitation is acknowledged; however, repeat testing and factor assays established that the abnormality was genuine.

Management Principles Guided by Phenotype Rather Than Laboratory Values

Management should therefore be guided by bleeding phenotype, history of hemostatic challenges, and procedural risk rather than FVII level or INR alone. For asymptomatic or mildly affected patients, clinical observation with individualized follow-up, education, avoidance of hemostasis-impairing medications, and clear emergency instructions are appropriate. [5] Replacement therapy is generally reserved for active significant bleeding, major trauma, major surgery, delivery in selected high-risk patients, or procedures with substantial bleeding risk. rFVIIa (recombinant activated Factor VII) is commonly preferred when available because it avoids volume overload and infectious risks associated with plasma products; however, thrombotic complications have rarely been reported, particularly in patients with additional thrombotic risk factors, so treatment should be individualized. [11] Fresh frozen plasma, plasma-derived FVII concentrates, or prothrombin complex concentrates may be alternatives depending on local availability and risk-benefit assessment. [3,11]

Special Considerations for Women of Childbearing Age

For women of childbearing age, counselling should include menstrual monitoring, reproductive counselling, and early pregnancy planning with hematology and obstetrics. Although this patient did not report menorrhagia, women with inherited bleeding disorders may present with heavy menstrual bleeding or postpartum hemorrhage, and management during pregnancy and delivery is heterogeneous. [12]

Table 2: Differential diagnosis of isolated prolongation of prothrombin time with normal aPTT.

Condition	Typical PT/INR	aPTT	Factor pattern	Mixing study	Key clinical/laboratory clues
Vitamin K deficiency	Prolonged	Normal or mildly prolonged	Reduced Factors II, VII, IX, and X	Usually corrects	Malnutrition, prolonged antibiotics, malabsorption, cholestasis, and low vitamin K intake
Liver disease	Prolonged	Normal or prolonged	Multiple coagulation factor deficiencies; reduced synthetic function	Usually corrects partially or completely	Abnormal liver enzymes, hypoalbuminemia, thrombocytopenia, portal hypertension
Warfarin exposure	Prolonged	Usually normal initially	Reduced vitamin K-dependent factors (II, VII, IX, X)	Corrects	Anticoagulant use, elevated INR in a therapeutic context
Acquired FVII inhibitor	Prolonged	Usually normal	Isolated low FVII activity due to an inhibitor	Fails to fully correct or shows time-dependent inhibition	Autoimmune disease, malignancy, severe systemic illness, unexpected bleeding
Congenital FVII deficiency	Prolonged (sometimes markedly)	Usually normal	Isolated low FVII activity	Corrects completely	Personal/family bleeding history, normal Factors II/IX/X, variable bleeding phenotype despite low FVII

aPTT, activated partial thromboplastin time; FVII, Factor VII; INR, international normalized ratio; PT, prothrombin time.

Role of Family Screening and Genetic Testing

Family screening with PT and FVII activity testing was recommended for first-degree relatives. F7 gene sequencing was not performed, which limits genotype-phenotype interpretation and cascade testing; however, in our case, the diagnosis is supported by the clinical presentation, complete correction on a mixing study, and isolated severe reduction in FVII activity.

Comparison Between This Case and Previously Published Reports of Patients With Congenital FVII Deficiency in Terms of Demographic and Clinical Characteristics

The demographic and clinical characteristics of the reported cases of patients with congenital FVII deficiency are described in **Table 3**.

This table compares the present case with representative previously published cohorts and registry reports of congenital FVII deficiency, emphasizing the marked heterogeneity of clinical presentation and the weak correlation between FVII activity level and bleeding severity.

This case has several limitations, including the absence of genetic confirmation, a lack of a standardized bleeding assessment score, and minimal discussion of long-term follow-up. These limitations hinder our ability to generalize our findings and underscore the need for larger case series to more accurately define genotype-phenotype correlations. Nonetheless, it contributes to current knowledge by illustrating that even markedly prolonged PT/INR levels can occur alongside a mild bleeding history and uncomplicated prior surgeries in individuals with congenital FVII deficiency.

Acknowledging this inconsistency is crucial to prevent unwarranted prophylactic treatment in stable patients, while still ensuring thorough planning for situations such as surgery, trauma, or pregnancy.

CONCLUSIONS

Isolated severe PT prolongation with normal aPTT should prompt a systematic evaluation that includes repeat sampling, exclusion of acquired causes, a mixing study, and specific factor assays. This case of severe congenital FVII deficiency with activity reported as <5.6% demonstrates that marked coagulation abnormalities and high INR do not necessarily predict major bleeding risk. Recognizing the frequent discordance between FVII activity and bleeding phenotype is crucial to avoid overtreatment while still ensuring careful planning for surgery, trauma, and pregnancy in affected individuals (**Figure 2**).

CONSENT

Written informed consent was obtained from the thr patient for the publication of this case report and all associated images.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by following the case at the bedside, conducting literature searches, drafting, revising, or critically reviewing the article.

Table 3: Comparison of the present case with previously published reports of congenital FVII deficiency.

Study/ reference	Age/sex	FVII activity	PT/INR severity	Main bleeding manifestations	Surgical/ procedural history	Clinical severity
Peyvandi et al. [6]	Mixed cohort (Italy/Iran)	Severe deficiency in many patients (<10%)	Markedly prolonged PT	Epistaxis, hemarthrosis, gastrointestinal bleeding, and intracranial hemorrhage	Variable	Wide phenotypic variability from mild to severe
Mariani et al. [4]	Registry cohort	Variable, including <10%	Variable PT prolongation	Mucosal bleeding, hemarthrosis, CNS bleeding, and asymptomatic cases	Some patients tolerated procedures without major bleeding	Poor correlation between FVII level and phenotype
Lapecorella et al. [9]	International registry data	Broad range	Variable	Cutaneous bleeding to life-threatening hemorrhage	Variable	Heterogeneous clinical presentation
Benlakhal et al. [13]	Surgical cohort	Mild to severe deficiency	Variable	Many patients are asymptomatic perioperatively	157 procedures performed without replacement therapy in selected patients	Some low-FVII patients tolerated surgery without prophylaxis
Napolitano et al. [5]	Review/ registry analysis	Often <10% in severe cases	Frequently marked PT prolongation	Menorrhagia, epistaxis, hemarthrosis, CNS bleeding, or asymptomatic	Variable need for prophylaxis	Bleeding phenotype poorly predicted by FVII level
Present case	21-year-old female	<5.6%	PT 96 s; INR 8.0	Recurrent spontaneous ecchymoses only	Uneventful septorhinoplasty and dental procedures	Mild phenotype despite severe laboratory abnormality

CNS, central nervous system; FVII, Factor VII; INR, international normalized ratio; PT, prothrombin time.

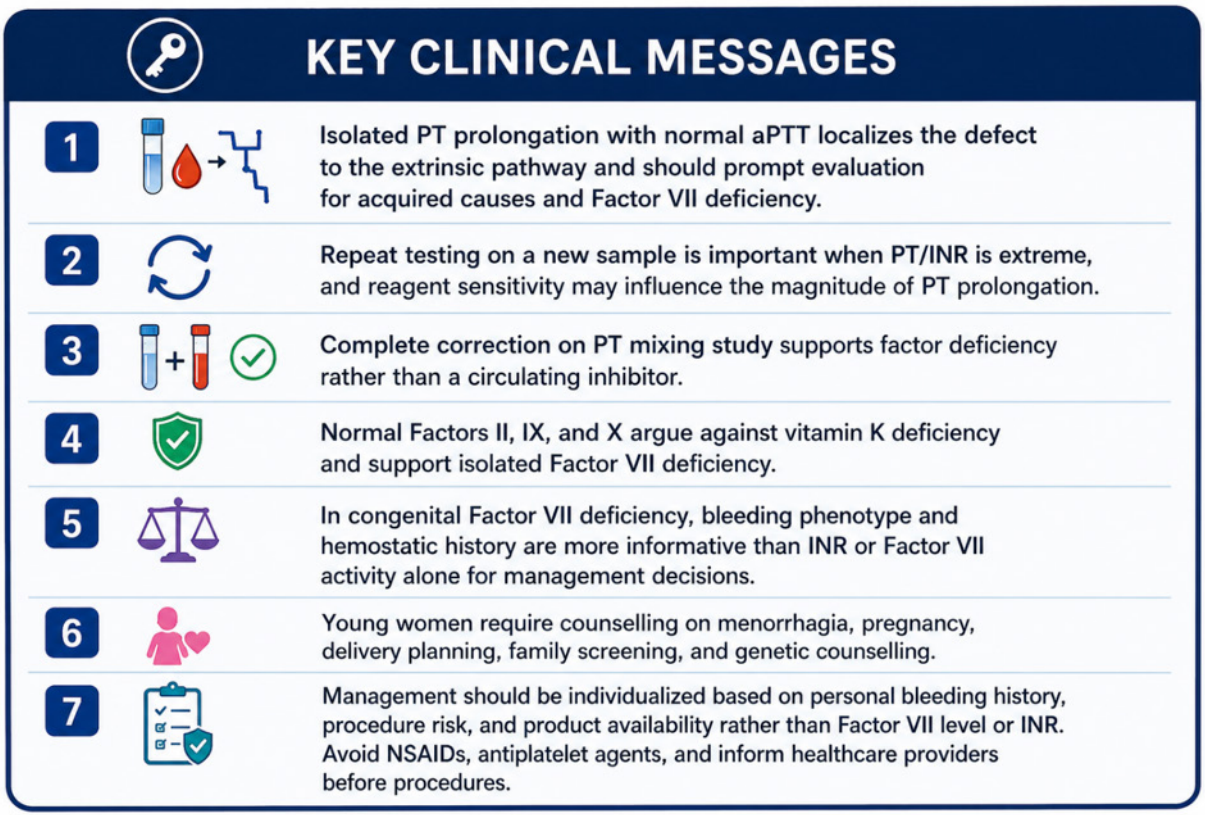

Figure 2: Key Clinical Messages in Congenital Factor VII Deficiency. Summary of the diagnostic approach, interpretation of isolated prolonged PT with normal aPTT, role of mixing studies and factor assays, phenotype–laboratory discordance, and key management principles..

They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

None.

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