Women and Inherited Bleeding Disorders

Disease background

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Overview – Women with bleeding disorders

1 in 100 women in the US may have an **undiagnosed bleeding disorder**[1]

In the US, **vWD is the most common** bleeding disorder reported in women[2]

Women often experience challenges with **delays in diagnosis**[2,3]

Women with bleeding disorders:

commonly experience HMB, leading to impaired HRQoL and issues with differential diagnosis[2,5]

are at increased risk of postpartum hemorrhage[6]

Hormonal therapy should be first-line treatment for women with vWD and HMB, if pregnancy is not desired, allowing for preservation of fertility[7]

Diagnosis of inherited bleeding disorders is important:[4]

- For the prevention and management of bleeding
- To improve quality of life and mental health
- To facilitate recommendations for invasive procedures, pregnancy, and delivery
- For family planning and genetic testing

In addition to HMB, women with inherited bleeding disorders can experience other bleeding symptoms throughout their life, leading to increased morbidity and impairment of daily activities[2]

HMB, heavy menstrual bleeding; HRQoL, health-related quality of life; US, United States; vWD, von Willebrand disease.

1. Rhynders PA et al. Am J Prev Med 2014;47:674–80; 2. Byams VR et al. Haemophilia 2011;17(Suppl 1):6–13; 3. Di Michele DM et al. Haemophilia 2014;20:e136–43; 4. National Hemophilia Foundation. MASAC #286. Available at: https://www.bleeding.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-286-masac-recommendations-regarding-diagnosis-and-management-of-inherited-bleeding-disorders-in-girls-and-women-with-personal-and-family-history-of-bleeding?menuid=57&contentid=1192. Accessed August 2024; 5. Rae C et al. Haemophilia 2013;19:385–91; 6. James AH. Haemophilia 2010;16(Suppl 5):160–7; 7. James AH et al. Haemophilia 2016;22(Suppl 5):54–9.

Women with hemophilia

Definition of the disease[1]

- Hemophilia A and B are congenital, X-linked recessive bleeding disorders caused by deficiency of coagulation FVIII and FIX, respectively

Prevalence and gender distribution[2–5]

- Although hemophilia primarily affects males since they only have one X chromosome, females with only one affected X chromosome can also have hemophilia
- As with males, females with FVIII/FIX levels <40% are classified as having mild/moderate/severe hemophilia, whereas women who exhibit bleeding symptoms and have FVIII/FIX levels >40% are considered symptomatic carriers of hemophilia

Symptoms[3,6,7]

- Excessive/spontaneous bleeding in joints (ankle, elbow, knee) and soft tissues (muscle, mucocutaneous), menorrhagia, ICH (life-threatening; usually traumatic in origin), retroperitoneal bleeding, episodic bleeding in GI tract, postoperative bleeding

Diagnosis[6]

- Family history and genetic screening tests
- Testing of FVIII or FIX activity is recommended prior to menstruation or surgery

Guidelines suggest that treatment recommendations for males also apply to women with hemophilia[4]

FIX, factor IX; FVIII, factor VIII; GI, gastrointestinal; ICH, intracranial hemorrhage.

1. Kumar R et al. Semin Thromb Hemost 2016;42:18–29; 2. World Federation of Hemophilia. Annual Global Survey Report 2022. Available at: https://www1.wfh.org/publications/files/pdf-2399.pdf. Accessed August 2024; 3. Srivastava A et al. Haemophilia 2020;26(Suppl 6):1–158; 4. Rezende SM et al. J Thromb Haemost 2024:22:2629–52; 5. van Galen KPM et al. J Thromb Haemost. 2021;19:1883–87; 6. Escobar MA, Key NS. Hemophilia A and hemophilia B. In: Kaushansky K et al., eds. Williams Hematology, 9e. McGraw-Hill Education; 2016; 7. Escobar MA. Products used to treat hemophilia: dosing. In: Lee CA et al., eds. Textbook of Hemophilia. Malden, MA: Blackwell Publishing; 2005.

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Additional considerations for women with hemophilia

Similar to males, females with hemophilia also experience joint and muscle bleeds, and higher risks of bleeds with surgery and dental procedures; however, it is also important to consider their increased risk of menorrhagia and additional complications associated with pregnancy and birth[1,2]

Stage of pregnancy	Considerations[1,2]
Early pregnancy	• Prophylaxis with vWF concentrate, desmopressin, and/or anti-fibrinolytics is indicated prior to uterine evacuation and other invasive procedures during pregnancy, such as chorionic villous sampling, amniocentesis, and cerclage
3rd trimester	• Assess fibrinogen, FVIII, and FIX levels
Delivery	• Vaginal delivery or early cesarean, **but** cesarean delivery should be considered if a potentially affected infant is expected • **AVOID** fetal scalp electrodes, fetal blood sampling, and forceps and vacuum extraction

A comprehensive childbirth plan created by a multidisciplinary team should be in place well before delivery because serious bleeds could result in adverse fetal outcomes[1]

FIX, factor IX; FVIII, factor VIII; vWF, von Willebrand factor.

1. Srivastava A et al. Haemophilia 2020;26(Suppl 6):1–158; 2. National Hemophilia Foundation. MASAC document #265. Available at: https://www.hemophilia.org/sites/default/files/document/files/265.pdf. Accessed August 2024.

von Willebrand disease

Definition of the disease[1]

- vWF mediates initial platelet adhesion and binds and stabilizes FVIII, protecting it from clearance
- vWD results from qualitative or quantitative defect in vWF
- vWD is classified into three major categories: partial quantitative deficiency (type 1), qualitative deficiency (type 2), and total deficiency (type 3)

Prevalence and gender distribution[1–3]

- Prevalence: ~1/100; equal distribution between men and women
- However, women are twice as likely to be diagnosed

Symptoms[2]

- Mild bleeding (type 1/2), hemorrhage during delivery, epistaxis, mucocutaneous bleeding, easy bruising, post-surgical bleeding, HMB (a high prevalence of HMB has been reported, ranging from 32% to 100% among women with vWD)

Diagnosis[2]

- Laboratory tests include: PFA-100 closure time, vWF antigen, functional vWF-dependent platelet adhesion (vWF:RCo), FVIII activity (FVIII:C)

Guidelines suggest using long-term prophylaxis rather than no prophylaxis in patients with a history of severe and frequent bleeds[4]

FVIII, factor VIII; FVIII:C, factor VIII coagulant activity; HMB, heavy menstrual bleeding; PFA, platelet function analyzer; vWD, von Willebrand disease; vWF, von Willebrand factor; vWF:RCo, von Willebrand ristocetin cofactor.

1. US Department of Health and Human Services/National Institutes of Health. The Diagnosis, Evaluation, and Management of von Willebrand Disease. Updated 2007. Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/vwd.pdf. Accessed August 2024; 2. James AH et al. Haemophilia 2016;22(Suppl 5):54–9; 3. World Federation of Hemophilia. Annual Global Survey Report 2022. Available at: https://www1.wfh.org/publications/files/pdf-2399.pdf. Accessed August 2024; 4. Connell NT et al. Blood Adv 2021;5:301–25.

Congenital FVII deficiency

Definition of the disease[1]

- FVII deficiency is one of the most common types of the rare coagulation protein deficiencies

Prevalence and gender distribution[1–4]

- Congenital FVII deficiency is a rare, inherited condition affecting an estimated 1 in 500,000 individuals
- Follows an autosomal inheritance pattern, affecting males and females equally
- Women with FVII deficiency exhibit a bleeding tendency similar to that observed in males

Symptoms[5]

- Epistaxis (60%), easy bruising (36%), gum bleeding (34%), menorrhagia (69%), hemarthrosis (19%), GI bleeding (15%), central nervous system bleeding (2.5%, can be the most serious and life-threatening symptom)

Diagnosis[6–9]

- Laboratory tests including prolonged PT, normal aPTT, normal thrombin time, low FVII activity level (<50%), FVII antigen levels

During pregnancy, factor replacement therapy is recommended when FVII <0.2 IU/mL in the last trimester, the patient has a history of bleeding, or cesarean section is required[10]

aPTT, activated partial thromboplastin time; FVII, factor VII; GI, gastrointestinal; PT, prothrombin time.

1. Di Minno G. Blood Rev 2015;29(Suppl 1):S26–33; 2. Napolitano M et al. Haemophilia 2016;22:752–9; 3. National Bleeding Disorders Foundation (formerly National Hemophilia Foundation). Factor VII. Available at: https://www.hemophilia.org/bleeding-disorders-a-z/types/other-factor-deficiencies/factor-vii. Accessed June 2022; 4. Mariani G, Bernardi F. Semin Thromb Hemost 2009;35:400–6; 5. Napolitano M et al. J Clin Med 2017;6:38; 6. van Herrewegen F et al. Eur J Pediatr 2012;171:207–14; 7. Mariani G, Dolce A. Rare bleeding disorders. In: Lee C et al., eds. Textbook of Hemophilia. Malden, MA: Blackwell Publishing Ltd; 2005:311–4; 8. Palla R et al. Blood 2015;125:2052–61; 9. Mariani G et al. Thromb Haemost 2005;93:481–7; 10. Mumford AD et al. Br J Haematol 2014;167:304–26.

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Congenital FXIII deficiency

Definition of the disease[1]

- FXIII circulates in the plasma as a heterotetramer composed of two A subunits and two B subunits. After activation by thrombin in the final phase of the clotting cascade, it cross-links fibrin, stabilizing the clot and protecting it from fibrinolysis
- FXIII deficiency results in the formation of an unstable clot and delayed bleeding cessation

Prevalence and gender distribution[2–4]

- Ultra-rare, autosomal recessive bleeding disorder (~1 case per 2–3 million people)
- Increased prevalence in countries in which consanguineous marriages are common
- All ethnicities and both genders are equally affected

Symptoms[5]

- Lifelong tendency of ICH, umbilical bleeding, hemarthrosis, miscarriage, muscle hematoma, postnatal bleeding, severe bruising, and bleeding after surgery or trauma

Diagnosis[6]

- Quantitative functional FXIII activity assay; establish subtype by measuring the FXIII-A2B2 antigen concentration. If decreased, the FXIII-A and FXIII-B subunits should be measured separately to determine the subtype

In addition to requiring regular replacement therapy, women with severe FXIII deficiency are at high risk of miscarriage and should receive more frequent prophylaxis during pregnancy[7,8]

FXIII, factor XIII; ICH, intracranial hemorrhage.

1. Karimi M et al. Semin Thromb Hemost 2009;35:426–38; 2. Anwar R, Miloszewski KJ. Br J Haematol 1999;107:468–84; 3. Schroeder V, Kohler HP. Semin Thromb Hemost 2013;39:632–41; 4. Dorgalaleh A, Rashidpanah J. Blood Rev 2016;30:461–75; 5. Bolton-Maggs PH et al. Haemophilia 2004;10:593–628; 6. Kohler HP et al. J Thromb Haemost 2011;9:1404–6; 7. Sharief LAT, Kadir RA. Haemophilia 2013;19:e349–57; 8. Mumford AD et al. Br J Haematol 2014;167:304–26.

Inherited platelet disorders

Definition of disease[1,2]

- Heterogeneous group of congenital bleeding diatheses associated with defects in platelet function or number
- Characterized by a wide phenotypic and genotypic heterogeneity
- Severity of bleeding differs based on the presence/absence of alternative pathways to complete clot formation

Symptoms[1]

- Mild to severe bleeding, muscle hematomas, central nervous system bleeds, hematuria, GI bleeds, and female-specific bleeding challenges

Diagnosis[1]

- Diagnosis includes complete blood count, blood smear, PFA-100, and other laboratory tests alongside genetic testing[1]
- Differential diagnosis testing is important[1]

Common Inherited Platelet Defects

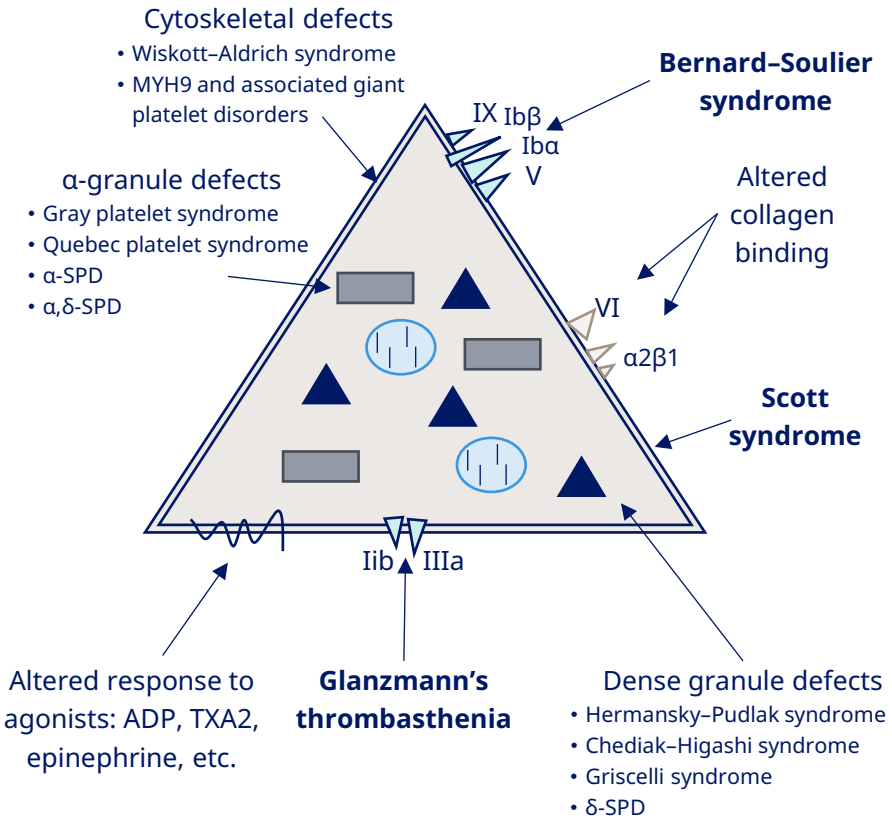

Figure adapted from Simon D et al. *Haemophilia* 2008;14:1240–9.

All patients should be managed by a specialist in comprehensive care clinics, and systemic hemostatic management is required for bleeding that fails local or adjunctive management, severe bleeding, and surgery[3,4,5]

ADP, adenosine diphosphate; α2β1, integrin alpha-2 beta-1; α-SPD, alpha-storage pool deficiency; α,δ-SPD, alpha-delta storage pool deficiency; δ-SPD, delta-storage pool deficiency; GI, gastrointestinal; Iba, glycoprotein Ib alpha; Ibβ, glycoprotein Ib beta; MYH9, myosin heavy chain 9; PFA, platelet function analyzer; TXA2, thromboxane A2.

1. Gresele P et al. Thromb Res 2019;181(Suppl 1):S54–9; 2. Simon D et al. Haemophilia 2008;14:1240–9; 3. Solh T et al. J Blood Med 2015;6:219–27; 4. Poon M-C et al. Expert Opin Orphan Drugs 2017;5:641–53; 5. Grainger JD et al. Br J Haematol 2018;182:621–32.

Glanzmann's thrombasthenia

Definition of the disease[1,2]

- A rare inherited bleeding disorder caused by a deficiency or dysfunction of the platelet membrane glycoprotein IIb/IIIa complex, leading to impaired platelet aggregation

Prevalence and gender distribution[1–3]

- Incidence is estimated at one in 1,000,000; with ~500 new cases reported globally
- Follows an autosomal inheritance pattern, affecting males and females equally
- More prevalent in populations in which consanguinity is common

Symptoms[1,2]

- Symptoms vary in severity, but often include easy bruising, epistaxis, HMB, gum bleeding, and bleeding after surgery/trauma

Diagnosis[2]

- Diagnostic tests include:
  - Complete blood count (normal platelet count, size, and granularity) and coagulation screening tests (PT and aPTT)
  - Platelet aggregation studies: Platelet light transmission aggregometry is the gold standard in clinical diagnosis of Glanzmann's thrombasthenia (decreased/absent aggregation [<10%] with all agonists except ristocetin)
  - Flow cytometry: Platelet glycoprotein expression study (decreased/absent [<20%] CD41 [GPIIb] and CD61 [GPIIIa])
  - Genetic testing (*after flow cytometry and platelet aggregation*): identify mutations in the ITGA2B or ITGB3 genes

Bleeding management is based on the use of hemostatic agents (rFVIIa, platelet transfusions, and antifibrinolytic agents), and comprehensive multidisciplinary care is essential for optimizing pregnancy outcomes[2,4]

aPTT, activated thromboplastin time; GI, gastrointestinal; GP, glycoprotein; HMB, heavy menstrual bleeding; ITGA2B, integrin alpha-IIb; ITGB3, integrin beta 3; PT, prothrombin time; rFVIIa, recombinant activated factor VII.

1. Nurden AT. Orphanet J Rare Dis 2006;1:10; 2. Botero JP, et al. Haematologica 2020;105:888–94; 3. Iqbal I et al. J Coll Physicians Surg Pak 2016;26:647–50; 4. Rottenstreich A, Coller BS. Br J Haematol 2024. doi:10.1111/bjh.19528. Epub ahead of print.

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Summary

In addition to the bleeding complications experienced by men with bleeding disorders, women with bleeding disorders may encounter added complications during menstruation, pregnancy, labor and delivery, and surgery[1]

Despite a substantial number of women being at risk or affected by inherited bleeding disorders, most do not receive care, with a global estimate of more than 1 million women likely not receiving adequate treatment[2]

Symptoms such as heavy menstrual bleeding are a common problem affecting women with bleeding disorders that can have a large impact on patients' lives[1]

To preserve quality of life, healthy reproduction, and social participation, women and girls with inherited bleeding disorders should receive treatment in conjunction with a multidisciplinary team[3,4]

Improvement in care for women with bleeding disorders is the focus of several organizations, such as: World Federation of Hemophilia, National Bleeding Disorders Foundation, Hemophilia Federation of America, and Foundation for Women & Girls with Blood Disorders[1,5–7]

1. National Bleeding Disorders Foundation (formerly National Hemophilia Foundation). Women and Bleeding Disorders. Available at: https://www.hemophilia.org/bleeding-disorders-a-z/overview/women-and-bleeding-disorders. Accessed August 2024; 2. Hermans C et al. Haemophilia 2024;30(Suppl 3):45–51; 3. Connell NT et al. Blood Adv 2021;5:301–25; 4. Mauser-Bunschoten EP et al. Haemophilia 2021;27:463–9; 5. US Department of Health and Human Services. Office of Women's Health: Bleeding Disorders. Available at: https://www.womenshealth.gov/a-z-topics/bleeding-disorders. Accessed August 2024; 6. Centers for Disease Control and Prevention. Bleeding Disorders in Women. Available at: https://www.cdc.gov/ncbddd/blooddisorders/women/index.html. Accessed August 2024; 7. World Federation of Hemophilia. Women and Girls with Hemophilia. Available at: https://www1.wfh.org/publications/files/pdf-2342.pdf. Accessed August 2024