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Chapter

Clinical Issues in Women with Inherited Bleeding Disorders

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Abstract

Various inherited bleeding disorders deserve careful medical management due to their implications in women's health. In both hemophilia A and B, almost exclusively, males are affected while carrier females are generally asymptomatic. Nevertheless, carriers may present important bleeding tendencies, which can eventually constitute a serious threat to life, especially after surgery or postpartum. In addition, in rare but significant cases, some genetic mechanisms have been found to cause hemophilia in females. Aside from von Willebrand disease, which is the most widespread and better described hemorrhagic condition in women, platelet disorders and some rare clotting deficiencies cause a wide variety of mucocutaneous bleedings, menorrhagia, or postpartum bleeding, hence constituting an important health risk. A review of the genetic and pathophysiological aspects as well as main clinical complications of all these conditions will allow for preventive practices aimed at improving the quality of life of women with bleeding disorders.

Keywords: symptomatic carriers and women with hemophilia, von Willebrand disease, platelet disorders, rare bleeding disorders, bleedings in pregnancy and postpartum

1. Introduction

Inherited bleeding disorders are a group of deficiencies including the decreased function or number of platelets (thrombocytopenia) and clotting factor deficiencies, mainly von Willebrand disease (VWD), hemophilia A (HA), and hemophilia B (HB), as well as rare bleeding disorders (RBDs) such as deficiencies of factors (F) I (fibrinogen), II, FV, combined FV-FVIII, FVII, FX, FXI, and FXIII and congenital deficiency of vitamin K-dependent factors and plasminogen activator inhibitor (PAI-1). Mostly autosomal recessive, together they have a prevalence of 1:500,000 to 1:1–3 million in the general population [1, 2].

Although all these entities cause bleeding tendencies in the affected males or females, there are relevant clinical issues related to obstetric and gynecological conditions that require special considerations in their management [1].

Menorrhagia or the more precise term of heavy menstrual bleeding (HMB) recommended by the International Federation of Gynecology and Obstetrics (FIGO)

is the most common symptom in women with bleeding disorders and is defined as bleeding that lasts more than 7 days or results in the loss of more than 80 mL of blood per menstrual cycle [1, 3]. In terms of women's quality of life, HMB is defined as "the excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life, and can occur alone or in combination with other symptoms; HMB is typically associated with a symptom complex, including variable pelvic pain and somatic symptoms" [3].

The FIGO also classifies the dysfunctional uterine bleeding disorders and identifies impaired hemostasis as one of the three recognized causes [3]. More than 70% of women with VWD present HMB and they are five times more likely to suffer from this complication than women without the condition. As for platelet disorders, the prevalence of HMB is 51% in women with Bernard-Soulier syndrome and 98% in women with Glanzmann thrombasthenia. HMB is present in 59% of women with FXI deficiency, in 57% of hemophilia carriers, and in 35–70% of women with other rare factor deficiencies [1].

In addition to HMB, women with bleeding disorders frequently suffer from large clots and flooding during their menstruation as well as bleeds after their menstrual period, conditions that may seriously affect their quality of life. Since 1990, Higham et al. proposed a pictorial blood assessment chart (PBAC) that was based on a validation study against the alkaline hematin method for blood measurement, which is known to be very accurate and reproducible but not practical in routine clinical use [4]. A score greater than 100, based on the number of used tampons or towels and the points assigned according to the estimated blood soaking, represents a very good prediction and considers a menstrual blood loss of more than 80 mL as positive HMB. The passage of clots and flooding episodes are also registered and considered for the score [1, 4].

HMB can be considered a significant symptom of a bleeding disorder, especially when it is present at menarche. The hematological evaluation of women with HMB should take into account the personal and familial bleeding history of epistaxis, easy bruising bleeding in the oral cavity, prolonged bleeding following dental extraction, unexpected post-surgical bleeding, hemorrhage requiring transfusion, and postpartum hemorrhage, especially after 24 h [1]. In patients with at least 2–3 symptoms, additional screening and confirmatory tests for VWD, platelet function, coagulation times, and clotting factor levels are mandatory [1].

Concerning the management of pregnancy and postpartum, women suspected of having a bleeding disorder or being a carrier of hemophilia should undergo diagnostic testing before getting pregnant in order to receive appropriate preconception counseling and early pregnancy management. This information allows for consideration of the available reproductive choices and options for prenatal diagnosis such as planning for pregnancy and establishing the best management in terms of hemostatic treatment and for the support of the pregnancy [1]. After the delivery, the elevated coagulation factor returns to the pre-pregnancy levels; therefore, the main risk of bleeding is after miscarriage or delivery. Postpartum hemorrhage (PPH) is a major cause of maternal morbidity and mortality, especially in developing countries or rural regions. PPH accounts for an estimated 140,000 maternal deaths each year worldwide and many women suffer from long-term debilitating consequences of the resultant anemia. Even if the most common causes of PPH are uterine atony, retained placenta, or genital tract trauma, coagulation disorders are also recognized causes of such complication [1].

In the next sections, we summarize clinical generalities, genetic aspects, impact on women's health, recommended treatment, and medical management of common inherited bleeding disorders.

2. Symptomatic hemophilia carriers

2.1 Generalities

Hemophilia is an X-linked disease due to mutations in the genes *F8* and *F9* (causing HA and HB, respectively) and subsequent deficiency of the clotting factors VIII (FVIII) and IX (FIX). HA affects 1/5000–10,000 males and HB 1/30,000 males. Both factors act in the same step of the coagulation mechanism and, when any of them is deficient, a diminished thrombin generation ensues. The symptoms have an inverse correlation with the plasmatic activity of the deficient factor, and the diagnosis and severity classification are based on the residual factor level [5].

2.2 Genetic aspects

Due to its recessive X-linked inheritance, males are mostly affected while the heterozygous female carriers are usually asymptomatic. Although some carriers have various bleeding manifestations and can even express severe (FVIII/FIX <0.01 U mL^{-1}) or moderate (FVIII/FIX 0.01–0.05 U mL^{-1}) phenotypes, their specific clinical manifestations and genetic data have hardly been described [6].

Hemophilia female carriers may be affected by hemorrhagic manifestations due to different genetic conditions: both mutated alleles with homozygous or compound heterozygous mutations in *F8* or *F9* genes, hemizygosity in 45,X (Turner syndrome) patients with a mutated X chromosome, or extremely skewed X-chromosome inactivation pattern (X-IP) in carriers who have inactivated the wild-type allele and thereby have a highly decreased amount of the concerned factor and express the symptoms of the disease [7]. The molecular genetic analysis is essential in elucidating the mechanisms underlying the bleeding phenotype in females with hemophilia [8–10].

In accordance with international estimations, there are 3–5 potential female carriers for each male with hemophilia, but not every carrier knows her genetic status. According to the study of Bernard, only 38% of the potential carriers have been screened about their carrier/non-carrier status. He analyzed 408 potential carriers and reported that only a limited fraction of them received information from a hemophilia specialist about their status and underwent coagulation factor analysis; the remaining large fraction failed to accomplish the screening due to lack of communication within the family and unawareness of the inheritance mode [11].

If women do not realize the possibility of being carriers, all their symptoms can be overlapped with normal women and those with VWD or qualitative platelet disorders [7]; so, all possible or potential carriers must be screened and should be advised about care and surveillance regarding bleeding tendencies [12].

2.3 Clinical features

Different studies have shown the increased tendency of bleeding in hemophilia carriers compared to healthy females. Olsson et al. described the bleeding symptoms in 126 hemophilia carriers in contrast to 90 non-hemophilia carriers; the hemorrhagic tendency was normal in 82 carriers (65%) and in all but two women in the control group (98%). They reported that there was no difference in bleeding symptoms between carriers from hemophiliac families and carriers with sporadic mutations. The proportion of carriers and controls reporting bleeding symptoms was different with statistically significant results ($p < 0.001$), **Table 1** [13].

Paroskie compared 44 HA carriers with 43 healthy women and found a significant ($p < 0.05$) increase in clinical features as shown in **Table 2** [5]. Contrary to

Clinical features	Carriers (%)	Controls (%)
Menorrhagia	37	16
Bleeding from minor wounds	32	0
Surgery	32	7.2
Tooth extraction	30	0
Nosebleed	24	4.4
Cutaneous bleeding	17	1.1

Taken from information reported by Olsson et al. [13].

Table 1.
Bleeding symptoms in hemophilia carriers and normal women.

Clinical features	Carriers (%)	Controls (%)
Heavy menstrual bleeding	70	5
Cutaneous bruising	65	40
Oral cavity bleeding	50	25
Post-surgical bleeding	48	9
Hematomas	35	8
Postpartum bleeding	30	8
Hemarthrosis	18	0

Taken from the study of Paroskie [5].

Table 2.
Clinical traits related to hemorrhages in hemophilia carriers and normal women.

what would be expected, laboratory results do not always correlate with the clinical picture. A comparison of FVIII:C/FIX:C levels, hemoglobin, platelets, and fibrinogen between symptomatic hemophilia carriers and asymptomatic carriers did not reveal significant differences, yet a subgroup of carriers with factor levels within the lower normal range exhibited increased blood symptoms [14].

Srivaths et al. compared the bleeding complications in adolescents and adults and found that anemia and gynecologic procedures/surgeries were less frequent in adolescents likely because of an early detection [15]. On the other hand, in the case of HB due to Hemophilia B Leyden mutation (c.-22T>C) in the promotor of *F9* gene, there is a physiological mechanism that tends to normalize the FIX plasma levels according to age, which is mainly mediated by growth hormones rather than androgens that may ameliorate the bleeding symptoms in patients and female carriers [16].

2.4 Impact on women's health

The time between the start of bleeding symptoms and the diagnosis of a FVIII/FIX deficiency is often prolonged. Di Michele et al. reported that the mean period of diagnosis for hemophilia carriers with severe FVIII/FIX deficiency was 8.5 months compared to 2 months for similarly affected males; but if the deficiency was moderate, the diagnosis was delayed for 48 months compared to 4 months for similarly affected men [6].

The most common symptom, HMB, can have a significant impact on quality of life, missed days at work/school, iron deficiency anemia, need for hospitalization or blood transfusions, and higher costs in medical care [7]. Delayed diagnosis situates affected women at risk for co-morbidity and even mortality depending on the

clinical context; this is why the carrier status and the percentage of clotting factor should be determined, and a proper genetic counseling should be offered [15].

2.5 Treatment

Dose, intervals, and duration for treatment depend on the clinical situation, effectiveness, and laboratory test results [7]. The treatment may include tranexamic acid, oral contraceptive pills (in some HMB), or factor VIII/IX [7, 15]. Hemostatic plans for hemophilia carriers with severe or mild FVIII/FIX deficiency should be noticed among primary care physicians and specialists in gynecology/obstetrics, hematology, orthopedics, clinical genetics, etc. Although each patient requires a personalized management, here we describe general guidelines for the treatment of the main hemorrhagic disorders in women:

2.5.1 HMB

Adolescents and women with HMB often respond well to standard therapies such as combined oral contraception pills, progestin-only pills, intrauterine devices, or antifibrinolytics such as aminocaproic acid or tranexamic acid. These therapies are warranted as the two key mechanisms in HMB are excessive local fibrinolytic mechanisms and inhibition of platelet function [7].

2.5.2 During pregnancy

The management of a hemophilia carrier should be coordinated among the hematologist, obstetrician, and anesthetist. During pregnancy, plasma levels of von Willebrand factor (VWF) and FVIII may rise sufficiently to permit safe hemostasis without exogenous hemostatic support, but they should be re-examined at 32–34 weeks of pregnancy; if the levels are less than 50% and more particularly less than 30% of the reference ranges, DDAVP or FVIII concentrates may be used. In pregnancy, FIX levels do not rise [17]. The use of DDAVP in symptomatic carriers of FVIII deficiency is controversial because the prescriber's information advises that the drug is contraindicated with lactation and recommends precaution during pregnancy. This drug has been used in the first and second trimester in 27 symptomatic carriers without adverse events [18]. Moreover, symptomatic carriers with factor levels less than 50% should receive a recombinant factor to prevent bleeding at delivery or spinal anesthesia [19]. Determination of fetal sex and prenatal hemophilia testing in any at-risk pregnancy are essential for planning the safe delivery of an affected female.

DDAVP is also indicated for HA patients with factor VIII coagulant activity levels greater than 5%. Intravenous dose is 0.3 μg/kg IV over 15–30 minutes (for pre-op, 30 minutes before the procedure). Intranasal administration is indicated for patients with FVIII levels >5% at a dose of 50 μg (if the patient's weight is <50 kg) or 300 μg (if weight ≥ 50 kg) 2 h before any surgical procedure [20].

2.6 Recommended integral management

Management of females represents a special challenge due to the risk of menorrhagia or postpartum bleeding, the large proportion (almost 40%) of unaware hemophilia carriers, and the medical inexperience of hemophilia in women.

The successful management in symptomatic hemophilia carriers requires the coordination of hematology, obstetrics/gynecology, orthopedics, and the coagulation laboratory as well as a complete education of the hemophilia carriers with

the aim of providing them the best available information on the risk of bleeding, genetic implications in the offspring, reproductive options, and antenatal management of the affected offspring and mother [19].

3. von Willebrand disease in women

3.1 Generalities

VWD is the most common inherited bleeding disorder with a worldwide prevalence of 1% [21], associated with mucocutaneous and postoperative bleeding that is caused by a qualitative or quantitative defect of the VWF [22], a glycoprotein that participates in primary and secondary hemostasis via platelet adhesion at the site of the endothelial injury and platelet aggregation with the formation of the platelet plug, not to mention its role in transporting and stabilizing the FVIII [23].

VWD does not present sex, ethnic, or geographic predilection; however, the number of symptomatic women is greater than that of men in most populations (ratio 2:1) due to menstrual and delivery bleeding disorders [24]. The International Society on Thrombosis and Hemostasis (ISTH) recognizes six types of VWD [25] depending on the amount and functional activity of VWF. There can be a partial or total quantitative defect (type 1 and 3) or a qualitative defect (type 2) [26]. Moreover, type 2 VWD is subdivided into 4 variants (2A, 2B, 2M, and 2N) based on the details of the patient's phenotype [27].

3.2 Genetic aspects

The *VWF* gene, also known as *VWD*, is located at 12p13.3 and has a length of 178 kilobases (kb), and its 52 exons are transcribed into a 9 kb mRNA that encodes a pre-pro-VWF protein of 2813 amino acids whose different domains interact with other proteins and perform specific functions [28]. The expression of the *VWF* gene is limited to endothelial cells and megakaryocytes [29]. Different mutations cause quantitative (VWD types 1 and 3) or qualitative (type 2) defects in the VWF protein. VWD mostly has an autosomal dominant inheritance; only types 3 and 2N (in some cases type 2A) are inherited in an autosomal recessive manner [22].

3.3 Clinical features

Clinical manifestations of VWD could arise only when a hemostatic challenge occurs and include the following main symptoms:

- Excessive mucocutaneous bleeding.
- Hematoma with minimal trauma.
- Recurrent and prolonged epistaxis.
- Gingival hemorrhage.
- Prolonged bleeding after some dental procedure, surgery, or trauma.
- HMB (the most common symptom in women) or prolonged or excessive bleeding after delivery.

- Gastrointestinal bleeding, particularly in patients with type 2A VWD.
- Patients with type 3 and type 2N VWD may have hemarthroses due to a low level of FVIII [30].

3.4 Impact on women's health

HMB occurs in approximately 80% of cases and is associated with significant co-morbidity, namely iron deficiency anemia, stress, and reduction in the quality of life affecting daily activities; in addition, it entails higher costs in medical care [31]. There is evidence that women with VWD have higher rates of postpartum hemorrhage and transfusions at the time of delivery compared to healthy women [32].

Under normal conditions, postpartum hemorrhage is controlled due to the progressive increased activity of VWF and FVIII during pregnancy that reaches its maximum level at the time of delivery and subsequently decreases to a baseline level in approximately 1 month [32]. In VWD patients, the amount, functional activity, and behavior of VWF vary according to the disease's type and FVIII concentration **Figure 1** [33]. Although the function of the placenta may be impaired, there are inconsistent results about the risk of abortion in women with VWD [34].

Under normal conditions, a doubling of the levels of FVIII and VWF (VWF: Ag) and functional activity of the VWF (VWF: RCo) can be observed. Patients with severe VWD type 1 (increased clearance) do not show a significant increase in levels of VWF and FVIII. On the other hand, in type 1 there is a progressive increase in VWF levels; however, it is not as high as in normal conditions. In type 2A, the functional activity of VWF remains low due to the absence of high molecular weight multimers, and in type 2M the ratio of VWF: Ag/VWF: RCo is affected due to the low increase in VWF: RCo. In type 2N, FVIII remains reduced due to the inability of the VWF to bind to FVIII. Taken from Castaman [33].

3.5 Treatment

Because VWD is the most common cause of HMB, appropriate tests (measurement of VWF: Ag and VWF: RCo) should be performed to establish an accurate diagnosis and the specific treatment for the disease [35].

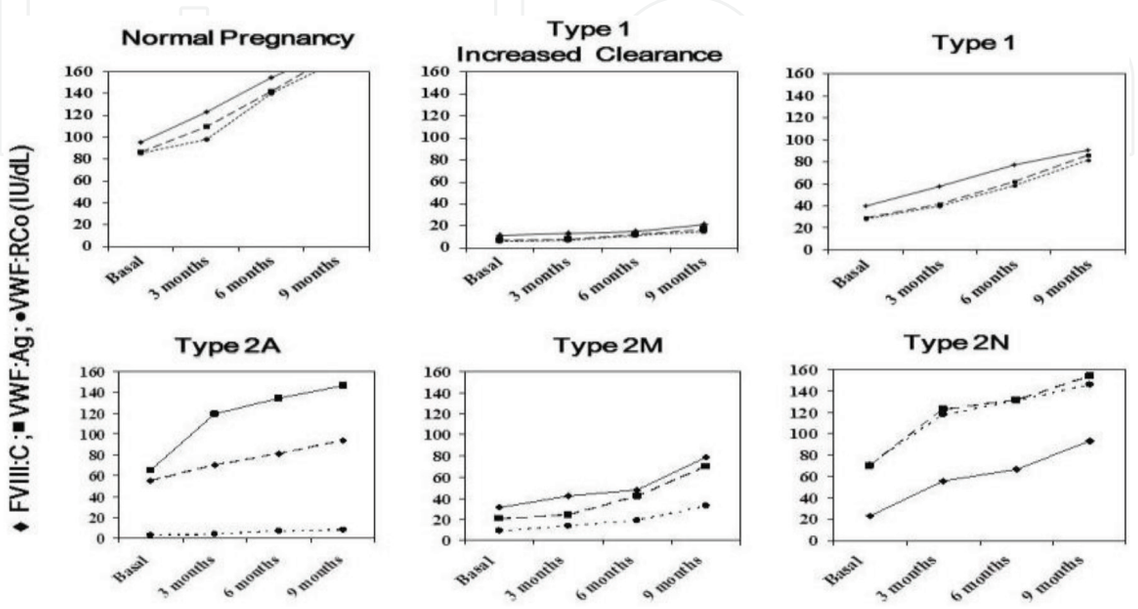


Figure 1.
Behavioral patterns of VWF and FVIII under normal conditions and in different VWD subtypes during pregnancy.

The treatment focuses on two central aspects: increasing the concentration of functional VWF available for hemostasis and providing complementary therapies to stabilize it [36]. DDAVP is administered intravenously or intranasally to increase plasmatic VWF through the release of endogenous VWF stored in Weibel-Palade bodies of endothelial cells. DDAVP is used in hemostatic challenges such as dental extractions and moderate nosebleeds or menorrhagia [36]. The administration of recombinant VWF is recommended in patients who do not respond to DDAVP or that require sustained levels of VWF in severe hemostatic challenges such as trauma and surgery [36]. Additional therapies include antifibrinolytic agents, amino-caproic acid, and tranexamic acid, which are recommended in mild to moderate bleedings. They are often used as adjunctive therapy in addition to concentrates of DDAVP or VWF in surgery or delivery [36].

3.6 Recommended integral management

Management in women presents a special challenge due to HMB and possible complications during pregnancy [37]. The successful management of pregnancy involves the coordination of obstetrics, anesthesia, and the coagulation laboratory that monitors levels of VWF: RCo and FVIII:C [37].

4. Platelet disorders

4.1 Idiopathic thrombocytopenic purpura (ITP)

4.1.1 Generalities

Idiopathic thrombocytopenic purpura or immune thrombocytopenia (ITP) is the most common acquired blood disorder. In this disease, autoantibodies against platelets render them susceptible to rapid clearance from the circulation [38–40]. Although the mechanism of origin of these antibodies is unknown, they belong to the gamma-globulin fraction expressed on platelet membranes and destroy the platelets [41–43] via their interaction with certain surface glycoproteins (GPs) identified as GP IIb-IIIa, GP Ib, and GP V [43]. The GP IIb-IIIa complex is the antigenic target in most patients. Platelets with antibodies are removed by splenic macrophages; however, their reactivation can lead to ineffective thrombopoiesis [40].

4.1.2 Genetic aspects

A positive family history is suggestive of hereditary thrombocytopenia. In addition to a presumptive autosomal dominant ITP, it has been found that the receptor for the Fc region of complexed immunoglobulin gamma (*FCGR2C*) predisposes to the disease [44, 45]. Several of their polymorphisms are related to the development of immunological reactions, but their contribution as a cause of ITP is still uncertain [46].

4.1.3 Clinical features

ITP can be acute or chronic and is characterized by (1) thrombocytopenia $<150 \times 10^9\ L^{-1}$ without other identifiable cause, (2) purpuric rash, and (3) normal function of bone marrow. Its approximate incidence is 3 to 8 per 100,000 children per year [43]. Acute ITP is frequent in children aged <10 years who have low platelet counts (usually 20,000 to $30 \times 10^9\ L^{-1}$). The onset of signs and symptoms is often

preceded by a viral illness. Chronic ITP affects mainly adolescents with platelet counts of 20-70×10^9 L^{-1}. Females are affected more frequently than males and are more likely to exhibit an underlying autoimmune disorder. Yet, the disease may be asymptomatic [43].

According to duration, ITP can be (1) newly diagnosed (<3 months), (2) persistent (between 3 and 6 months), or (3) chronic (>12 months). The clinical presentation can be (1) severe, patients with relevant bleeding, or requiring additional interventions or increased drug dose, or (2) refractory, severe clinical manifestations after splenectomy. Platelet counts define two types: (1) ≥100×10^9 L^{-1} measured on 2 occasions with more than 7 days between each sampling and (2) ≥30×10^9 L^{-1} and a greater than twofold increase in platelet count measured on 2 occasions >7 days apart [47].

Typical clinical presentation affects apparently healthy individuals; begins with easy bruising and purpuric rash [40]; and evolves to nasal, gingival, gastrointestinal tract, vaginal, urinary tract, retina, or conjunctivae bleedings. Bone marrow smears show normal or increased megakaryocytes, whereas plasma thrombopoietin levels are decreased. Patients with 10-20×10^9 L^{-1} of platelet counts are at increased risk for intracranial hemorrhage (ICH) [43].

4.1.4 Impact on women's health

About 7% of pregnancies or 1-10 in 10,000 pregnant women are diagnosed with gestational ITP (<150×10^9 L^{-1} of platelet count) generally in the first trimester [48, 49]. Only near 30% requires treatment and support from a multidisciplinary team [39, 50]. Recommended first-line therapy is intravenous immunoglobulin or corticosteroids, which have similar efficacy for platelet count increase. The latter may have mild toxicity for the mother and fetus, but usual adverse effects include weight gain, hyperglycemia, and hypertension [39].

4.1.5 Treatment

The pharmacologic management of acute ITP continues being controversial, because in approximately 80% of patients the disease is self-limited and disappears in the first 6 months after diagnosis without medication. For the 20% of patients who progress to the chronic type [43], prednisone at a standard dose of 1 mg/kg/day for 2–4 weeks is the first choice drug [39]. Yet, a randomized clinical trial has shown that it is better to use high-dose pulsed dexamethasone (40 mg/day for 4 days) than standard prednisone therapy in adult patients with immune thrombocytopenia [51].

4.1.6 Recommended integral management

Integral management of a patient with ITP is based on support measures (reduce physical activity, wear protective head-gear, adapt protective padding to the crib, avoid medications that affect platelets, and keep a constant evaluation and dental care) sometimes complemented with pharmacological and surgical treatment [43]. Patients require consulting a hematologist.

4.2 Bernard-Soulier syndrome

4.2.1 Generalities

Bernard-Soulier syndrome (BSS) results from a deficiency of platelet glycoprotein protein Ib (GPIb), which mediates the initial interaction of platelets

with the subendothelial components via the von Willebrand protein. It is a rare but severe bleeding disorder in which platelets do not aggregate in response to ristocetin. Platelets from BSS patients lack a major surface membrane glycoprotein complex called GPIb-IX-V that functions as a receptor for VWF and whose absence causes giant platelets [52]. This complex is the initial contact for adhesion of platelets in damaged vessels, mediates the interaction with VWF (GPIb-IX-V/VWF), and interacts with the platelet cytoskeleton [52, 53]. The GPIb-IX-V complex comprises GPIbα, GPIbβ, GPIX, and GPV proteins whose assemblage forms the receptor [54].

4.2.2 Genetic aspects

BSS usually results from autosomal recessive mutations in *GP1BA, GP1BB*, and *GP9* genes that code for 3/4 proteins of the GPIb-IX-V complex (mutations in the 4th gene involved, *GP5*, are unreported) [52, 54]. Compound heterozygous patients outnumber homozygous patients. Only a few cases result from autosomal dominant mutations [55]. Although BSS carriers are usually asymptomatic with normal platelet counts, sometimes they show slightly enlarged platelets, slightly decreased GPIb-IX-V complex expression, and/or a moderately reduced ristocetin response [55, 56].

4.2.3 Clinical and hematological features

Clinical presentation of BSS is characterized by epistaxis, gingival and cutaneous bleeding, hemorrhages post trauma, prolonged skin bleeding time, thrombocytopenia, and large platelets. Patients often suffer from mucocutaneous bleedings of different severity [54]. In females, it can be associated with severe menorrhagia [52]. Typically, platelet counts are low, and the platelets are so large (often the size of red blood cells) that they may be missed on blood counts because most automatic counters do not count them as platelets [40]. The clinical laboratory assessment of GPIb-IX-V/VWF interaction with platelets reveals impaired platelet agglutination after stimulation with ristocetin [52, 54, 57].

4.2.4 Impact on women's health

Some women with BSS require oral contraceptive treatment for menorrhagia and even platelet transfusions in cases of severe bleeding [57]. Generally, pregnancies of patients with BSS are not complicated [58]. However, if during the delivery the patient presents severe bleeding, platelet transfusions or hysterectomy can be performed to control it [59].

4.2.5 Treatment

Usually, platelet transfusions are effective as BSS treatment; the inconvenience is the alloantibody development against GpIb [56]. Transfusions must be used only for severe bleeding and emergencies [40]. Also, the use of DDAVP, epsilon-aminocaproic acid (EACA), and recombinant factor VIIa (rVIIa) has been approved as an effective therapy for some patients [56].

4.2.6 Recommended integral management

BSS care is generally based on support measures only, inclusive for dental care. Actually, most patients do not require medication. The use of antiplatelet treatment must be avoided, and a hematologist should be consulted for its prescription [60].

4.3 Glanzmann thrombasthenia

4.3.1 Generalities

Glanzmann thrombasthenia (GT) is a rare dysfunction of the platelet integrin receptor CD41 (GPIIb/IIIa complex) that prevents the formation of aggregates in response to many agents, except for ristocetin [40, 56]. There are two GT types according to the functionality of the GP IIb/IIIa complex; type I is caused by the total absence of the GP IIb/IIIa complex and exhibits a more severe phenotype; type II is usually milder because some of the GP IIb/IIIa complexes are functional [40].

4.3.2 Genetic aspects

GT is an autosomal recessive disorder due to diverse mutations of the multi-subunit GpIIb/IIIa complex [56, 61–63]. The carriers or heterozygotes are asymptomatic, although they show a 50% reduction in the number of GpIIb/IIIa molecules [56]. *ITGA2B* and *ITGB3* genes code for proteins GPIIb and GPIIIa, respectively, and both are located at 17q21 [64]. GT is frequent in regions where consanguineous marriages are common [65, 66].

4.3.3 Clinical features

Clinical manifestations are variable in severity and frequency and depend on the genotype. Bleeding symptoms are present in patients homozygous or compound heterozygous for GPIIb/IIIa mutations [67]. As a minimum symptom, the patients have lifelong mucosal bleeding [56]. The bleeding (epistaxis, gingival hemorrhage, and menorrhagia) can be frequent, severe, and sometimes fatal [62, 68]. Severe epistaxis is common, mainly in childhood. Some patients only had bruising. Less commonly, gastrointestinal bleeding and hematuria have been observed [69]. The platelet count, morphology, and size are normal [56].

4.3.4 Impact on women's health

The transfusion history of red cell and/or platelet is frequent. Affected women are at risk of severe HMB and bleeding during pregnancy and delivery [69].

4.3.5 Treatment

The standard treatment for continuous bleeding has been platelet transfusions, especially for patients refractory to local measures and/or antifibrinolytic drugs [70]. However, the efficacy of platelet transfusion is limited by alloantibodies against platelets [56]. Several authors of clinical trials recommend the use of rFVIIa in the management of intractable epistaxis. It has been documented that this agent is effective in the management of bleeding or during surgeries at doses from 120 to 300 μg/kg [71, 72].

4.3.6 Recommended integral management

GT is a hemorrhagic lifelong disorder that requires integral support measures. Most patients have a history of transfusions indicated for severe bleeding [40, 67]. Fortunately, the prognosis of patients is good due to supportive care, and the disease has limited effect on their daily lives [69]. Dental and hematological advice is recommended.

5. Rare bleeding disorders (RBDs) in pregnancy and postpartum

5.1 Generalities

RBDs account for 3–5% of all inherited coagulation conditions and are characterized by a wide variability of bleeding symptoms that range from mild to severe in individuals affected by the same disorder. Most commonly, mucocutaneous bleeding and post-surgery hemorrhage are observed. Affected women usually suffer from menorrhagia, spontaneous abortion, and bleeding after delivery [73]. Although most RBDs are autosomal recessive traits, some cases of FXI deficiency and hypo- and dysfibrinogenemia are autosomal dominant. According to the epidemiological data of the World Federation of Hemophilia (WFH) and European Network of the Rare Bleeding Disorders (EN-RBDs), the prevalence of each deficiency among the total affected population is as follows: FVII (39%), FXI (26%), Fibrinogen, FV and FX (8–9%), FXIII (6%), combined FV + FVIII (3%), and FII (1%) [73].

Medical management and treatment of the RBSs are suboptimal because of their very low frequency. As a result, affected individuals received delayed diagnosis, incomplete laboratory testing, and limited treatment options. Standardization of coagulation assays, global clotting assays, and genomic sequencing promises to improve the diagnosis of RBDs, but there is still a long gap to overcome [1]. **Table 3** shows a general scope of the physiological characteristics, symptoms, and impact of the RBDs.

Deficiency	Plasma level (μg/mL)	Bleeding symptoms	Laboratory diagnosis	Prevalence	Gene (chromosome)
Fibrinogen	1500–4000	Umbilical cord, hemarthrosis, mucosal tract, menorrhagia, first trimester abortion, CNS Venous, and arterial thromboembolism are reported	*Afibrinogenemia:* APTT↑↑, PT↑↑, TT↑↑, *dys-hypofibrinogenemia*: APTT↑, PT↑↑, TT↑↑	1:1,000,000	*FGA, FGB,* and *FGG* (4q28)
F II	100	Umbilical cord, hemarthrosis, and mucosal tract	APTT↑↑, PT↑ TT normal	1:2,000,000	*F2* (11p11-q12)
F V	10	Mucosal tract and postoperative	APTT↑, PT↑, TT normal	1: 1,000,000	*F5* (1q24.2)
F VII	0.13–1.0	Mucosal tract, hemarthrosis, hematomas, and neonatal CNS hemorrage	APTT normal, PT↑, TT normal	1: 500,000	*F7* (13q34)
F X	10	Umbilical cord, hemarthrosis, hematomas, and CNS hemorrhages	APTT↑, PT↑, TT normal	1: 1,000,000	*F10* (13q34)
F XI	3–6	Oral cavity, post-traumatic, and postoperative	APTT↑, ↑T, PT normal, TT normal	1: 1,000,000	*F11* (4q35.2)

Deficiency	Plasma level (μg/mL)	Bleeding symptoms	Laboratory diagnosis	Prevalence	Gene (chromosome)
F XIII	10–20	Umbilical cord, spontaneous CNS hemorrhages, miscarriages, and abnormal scarring	APTT normal, PT normal, TT normal specific FXIII assay	1: 2,000,000	*F13A1* (6p24-p25) *F13B* (1q31-q32.1)
FV + FVIII	As for each factor	Mucosal tract and postoperative	APTT↑, PT↑, TT normal	1: 1,000,000	*LMAN1* (18q21.3-q22) *MCFD2* (2p21-p16.3)
VKCFD	As for each factor	Umbilical cord, CNS hemorrhages, and postoperative (children may show skeletal abnormalities)	APTT↑, PT↑↑, TT normal	<50 families	*GGCX* (2p12) *VKORC1* (16p11.2)

CNS, central nervous system; APTT, activated partial thromboplastin time; PT, prothrombin time. Taken from Castaman and Linari [73].

Table 3.
Clinical symptoms and laboratory/molecular diagnosis in rare bleeding disorders (RBDs).

5.2 RBDs in pregnancy, delivery, and puerperium

Women with RBDs require especial medical treatment and care. In addition to common bleeding symptoms, they may also experience gynecological bleeding and are at increased risk of hemorrhagic ovarian cysts, endometriosis, and endometrial hyperplasia polyps and fibroids. Pregnancy and childbirth in women with RBDs are real clinical challenges; miscarriages, bleeding during pregnancy, and postpartum hemorrhage are frequent and may represent severe clinical complications [74].

There has been a higher risk of diverse obstetric complications reported in women with RBDs; miscarriage and placental abruption resulting in fetal loss or preterm delivery are rather common in women deficient in fibrinogen or factor XIII (FXIII) [1].

To resolve the clinical complications of women with RBDs, it is important to consider the behavior of the clotting factors in normal conditions and their tendency to increase during pregnancy that has been attributed to the increase of estrogen concentrations, especially in the third trimester (fibrinogen, FVII, FVIII, FX, FXII, FXIII, and VWF). Other factors (FII, V, IX, and XIII) increase slightly or remain unchanged while FXI is the only factor that decreases during pregnancy [75].

6. Conclusion

Inherited bleeding disorders may seriously impact the women's quality of life through their detrimental effects on academic, professional, and social life. Long-lasting HMB causes iron deficiency anemia with consequences on physical and mental well-being. Medical care for women with bleeding disorders is lacking in many countries and there may be cultural taboos and obstacles preventing women

from seeking help, specifically for menstrual problems, which may lead to marital disharmony and possibly fertility problems. Caregivers are often unaware about bleeding disorders in women, and therefore, even when women do seek help, the diagnosis is often neglected and appropriated treatment is not provided. In addition, bleeding disorders in women have negative consequences on the nutrition and well-being of their children. Early identification of young girls and women with HMB for managing their menstruation and iron deficiency is crucial in improving women's health in general [1].

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Conflict of interest

All the authors declare that there is no conflict of interest regarding their contribution to this chapter.

Appendices and nomenclature

BSS	Bernard-Soulier syndrome
DDAVP	1-deamino-8-D-arginine vasopressin, denominated as desmopressin
EACA	epsilon-aminocaproic acid
FCGRC2	receptor for the Fc region of complexed immunoglobulin gamma
FIGO	The International Federation of Gynecology and Obstetrics
FIX:C	factor IX procoagulant activity
FVIII:C	factor VIII procoagulant activity
FXIII	factor XIII protein
F8	factor 8 gene
F9	factor 9 gene
GPIb	platelet glycoprotein protein Ib
GPs	platelet surface glycoproteins
GT	Glanzmann thrombasthenia
HA	hemophilia A
HB	hemophilia B
HMB	heavy menstrual bleeding
ICH	Intracranial hemorrhage
ISTH	International Society on Thrombosis and Hemostasis
ITP	idiopathic thrombocytopenic purpura or immune thrombocytopenia
IVIg	Intravenous immunoglobulin
Kb	Kilobases
PAI-1	plasminogen activator inhibitor
PBAC	pictorial blood assessment chart
PPH	postpartum hemorrhage
RBDs	rare bleeding disorders
rVIIa	recombinant factor VIIa

VWD	von Willebrand disease
VWF	von Willebrand factor
VWF:Ag	antigen test of the VWF used to measure the amount of VWF
VWF:RCo	a ristocetin cofactor test used to measure functional activity of the VWF

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