HEMOSTASIS AND THROMBOSIS

Review

Rare inherited autosomal bleeding disorders in women: sex-related bleeding, pregnancy and delivery. A narrative review

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Rare inherited autosomal bleeding disorders (RAIBDs) are a heterogeneous group of coagulation diseases including rare bleeding disorders and inherited platelet disorders, characterized by a wide variability in frequency and severity of hemorrhagic symptoms. The management of women suffering from these disorders is very challenging due to sex-related bleeding, such as menstrual flow and hemorrhage events linked to pregnancy and delivery. Furthermore, in this subset of patients, there are open issues regarding the delivery mode, to preserve the newborn who could be affected by the same bleeding disorder. The purpose of this review is to explore evidence on the management of women suffering from RAIBDs in order to guide physicians taking care of this subset of patients.

Heavy menstrual bleeding (HMB) is often the most frequent reported symptom and the reason for referral: its lack of prompt identification can lead to a delay of diagnosis; HMB often provokes iron-deficiency anemia, with a significant reduction of quality of life. HMB treatments are limited and based on limited efficacy data. The rarity of these coagulation defects poses a challenge in the management of pregnancy and delivery, especially if the bleeding disorder is not diagnosed prior to the physiological pregnancy-associated changes in hemostasis (which make the diagnosis more difficult); a careful collection of the hemorrhagic and family history is essential. Currently, there is only limited evidence about the management of RAIBDs during pregnancy and delivery, and the present clinical practice is often based on the current local policy.

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INTRODUCTION

Inherited bleeding disorders (IBDs) are a heterogeneous group of coagulation diseases, characterized by a wide variability in frequency and severity, with autosomal and X-linked inheritance. Rare autosomal IBDs (RAIBDs) include rare bleeding disorders (RBDs): congenital fibrinogen disorders, congenital deficiency of Factors II, V, VII, X, XI and XIII, combined deficiency of the Factors V and VIII and combined vitamin

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K-dependent clotting factors deficiency and inherited platelet disorders (IPDs) (**Table I**)[1]. Women affected by RAIBDs must face some additional problems with respect to male patients with the same disorders, such as heavy menstrual bleeding (HMB: a total blood loss volume greater than 80 mL) and post-partum hemorrhage (PPH: a blood loss ≥500 mL with vaginal delivery or ≥1,000 mL with cesarean delivery)[2-4]. HMB has a strong impact on women's quality of life, being able to determine discomfort and iron-deficiency anemia. On the other hand, pregnancy and delivery are important challenges that impose a careful and multidisciplinary approach[5]. Therefore, compared to men, women suffer a delay in diagnosis and a reduced tendency to be treated with hemostatic prophylaxis[6]. RAIBDs in women are, for these reasons, a clinical but also a socioeconomic problem. Since interest has recently grown about sex-specific issues in women affected by RAIBDs, the aim of the present review is to analyze the current evidence about RAIBDs in women, focusing mainly on sex-specific bleeding and on the management of pregnancy and delivery in this subset of patients. The rarity of bleeding disorders is a diagnostic challenge mainly during pregnancy when hemostatic changes occur physiologically (**Table II**)[7].

Table I - *Estimated prevalence of rare inherited autosomal bleeding disorders*[43]

Deficiency	Estimated prevalence
Fibrinogen	1 in 1 million
Prothrombin	1 in 2 million
Factor V	1 in 1 million
Combined Factor V and Factor VIII	1 in 1 million
Factor VII	1 in 500.000
Factor X	1 in 1 million
Factor XI	1 in 1 million
Factor XIII	1 in 2 million
Vitamin K-dependent coagulation factors	Reported in <50 families
Inherited platelet function disorders	1 in 1 million

Table II - *Hemostatic changes during pregnancy (modified from* [7]*)*

Hemostatic parameter	Change at term pregnancy (% change)
Factors II, V and IX	No change
Fibrinogen	More than 100% increase
Factor VII	Up to 100% increase
Factors VIII, X, XII and VWF	More than 100% increase
Factor XI	Variable
Factor XIII	Up to 50% decrease
Platelet count	Up to 20% decrease

VWF: von Willebrand factor.

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DIAGNOSTIC WORKFLOW FOR SUSPECTED RAIBDS

Early recognition of rare RAIBDs requires a pragmatic, stepwise pathway that can be applied even in non-specialized hospitals. **Figure 1** summarizes our diagnostic workflow. Below, we outline the core principles and technical aspects of the most employed coagulation assays: prothrombin time (PT) is performed by incubating citrated plasma with a thromboplastin reagent (containing tissue factor and phospholipid) and calcium. Clot formation time is measured, typically by optical or mechanical detection. PT assesses the extrinsic and common coagulation pathways, primarily Factors VII, X, V, II, and fibrinogen[8]. For activated partial thromboplastin time (aPTT) citrated plasma is mixed with a contact activator (e.g., silica, kaolin) and phospholipid, then incubated. Calcium is added to initiate clotting, and the time to clot formation is measured. aPTT evaluates the intrinsic and common pathways (Factors XII, XI, IX, VIII, X, V, II, and fibrinogen)[9]. The mixing test is performed with a mixture of patient plasma with normal pooled plasma; the clotting test is repeated on the mixture. A correction of the clotting time suggests a factor deficiency; lack of correction indicates an inhibitor[10]. Interpretation may use percent correction or the Rosner index; incubation may help to distinguish time-dependent inhibitors (e.g., Factor VIII inhibitors) from immediate-acting inhibitors (e.g., lupus anticoagulant)[11].

In the single factor "one stage" assays patient plasma is mixed with a commercial plasma specifically deficient in the factor of interest; the mixture is tested using PT (for Factors II, V, VII, X) or aPTT (for Factors VIII, IX, XI, XII): the degree of correction of the prolonged clotting time is compared to a known factor level calibrator to quantify factor activity[12].

RARE BLEEDING DISORDERS

Sex-specific bleeding in Factor VII deficiency

Congenital Factor VII deficiency is a heterogeneous hemorrhagic disorder, with variability in the clinical

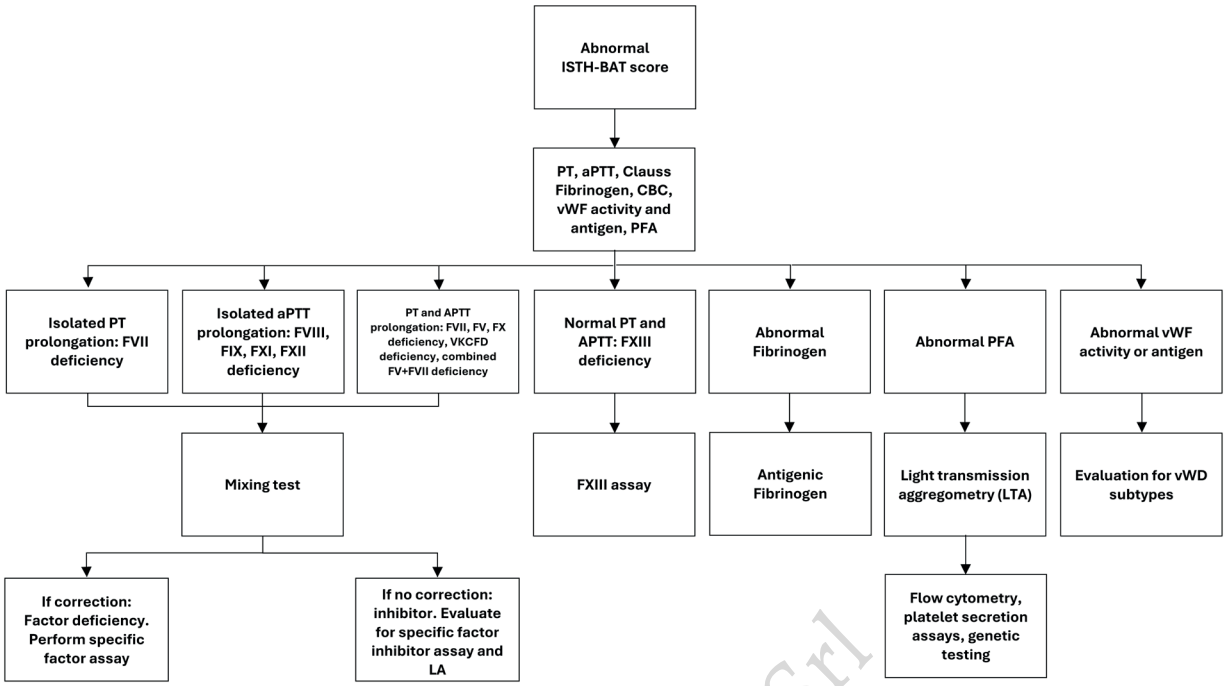


Figure 1 - Diagnostic flowchart for suspected RAIBDs
ISTH-BAT: International Society on Thrombosis and Hemostasis Bleeding Assessment Tool; PT: prothrombin time; aPTT: activated partial thromboplastin time; CBC: complete blood count; vWF: von Willebrand Factor; PFA: platelet function assay; VKCFD: vitamin K-dependent clotting factor deficiency; vWD: von Willebrand disease.

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phenotype that can range from asymptomatic or mild forms to severe conditions as there is no linear association between the level of residual factor and clinical hemorrhagic disease[13]. The most frequent symptoms are epistaxis, tendency to bruising, gum bleeding, post-operative bleeding. However, gastrointestinal or central nervous system (CNS) bleeding, muscle hematomas and hemarthrosis are described in the most severe forms. Spontaneous or iatrogenic thrombosis has been reported in 3-4% of patients[1].

HMB is reported in 50-69% of affected women and represents the symptom at onset in 12% of cases[14,15]. Antepartum bleeding, PPH and the presence of hemorrhagic ovarian cysts are also frequent in this subset of patients. Moreover, it is also possible to have an increased incidence of endometriosis and metrorrhagia[16]. In most cases, HMB is responsive to hormonal therapy or antifibrinolytics, but it is pivotal to monitor iron deficiency and anemia carefully[15]. In severe and recurrent forms of HBM, prophylaxis with recombinant activated Factor VII (rFVIIa) may be indicated: despite the short half-life of Factor VII, it has been demonstrated that a dosage of 20-40 mcg/kg 2-3 times a week represents an effective prophylaxis against bleeding[17]. A plasma-derived concentrate is also available, and it has been demonstrated to be safe and effective (15-40 IU/kg); being a non-activated FVII, it could be the safest option in pro-thrombotic settings such as pregnancy[18]. During pregnancy, Factor VII levels in healthy women increase up to 4 times the baseline value[19]; they can also increase in deficient heterozygotes with slightly or moderately low levels, reaching the maximum value in the third trimester, while in deficient homozygotes Factor VII levels do not increase[20]. In patients with Factor VII deficiency, bleeding may occur during pregnancy, but PPH is more frequent in this subset of patients: in a retrospective study analyzing 94 pregnancies, a PPH frequency of 10-13% was reported[21]. An increased risk of spontaneous abortion is unlikely in these patients, even though antepartum bleeding due to retro-placental hematomas or vaginal hemorrhages has been described in some patients with severe factor deficiency[22].

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Sex-specific bleeding in Factor XI deficiency

Inherited Factor XI deficiency presents a high clinical phenotypic heterogeneity: in fact, there is no correlation between the level of residual factor and the severity of the hemorrhagic picture. Patients with severe deficiency are at high risk of bleeding but may remain asymptomatic for life, while mildly deficient patients may experience significant bleeding after trauma or surgery[1]. However, there is an association between the factor deficiency and bleeding in anatomical areas with high antifibrinolytic activity (upper airways and digestive tracts, genitourinary tract, etc.). The most frequent clinical manifestations are therefore oral, post-traumatic and post-surgical bleeding. HMB is common in women deficient in Factor XI, and post-partum hemorrhage may affect up to 20-30% of them[23]. Treatment is also based on fresh frozen plasma (FFP) and on Factor XI plasma-derived concentrate, even though some cases of potentially life-threatening thromboembolic complications have been observed in patients with cardiovascular risk factors and for this reason they should be used only in selected cases of severe deficiency (<30%) in the absence of pre-existing cardiovascular diseases[24].

Sex-specific bleeding in Factor XIII deficiency

Clinical manifestations of Factor XIII deficiency include prolonged bleeding from wounds, soft tissue hemorrhages, spontaneous CNS hemorrhages (incidence up to 30%), which represent the main cause of death in these patients[17]. In severe disease, bleeding may occur from birth, with the umbilical cord separation, or with intracranial hemorrhages in the neonatal period (especially in relation to operative delivery); milder forms (heterozygotes) may, instead, remain asymptomatic until adulthood, and present with bleeding following trauma or surgery[17].

In women with Factor XIII deficiency, HMB is present in 28% of cases (second most frequent symptom after umbilical cord bleeding) according to Sharief *et al.*[25]. Regarding pregnancy, there is now consolidated evidence that Factor XIII plays an important role in implantation (for the formation of cross-linking bonds necessary for the attachment of the placenta to the uterine tissue); the lack of Factor XIII in the placenta causes implantation failure and pregnancy loss at a very early stage due to insufficient formation of the cytotrophoblastic shell[26]. According to Sharief *et al.*, 66% of the 192 pregnancies resulted in a miscarriage (mainly between 8 and 12 weeks of gestation); 25% of the women suffered recurrent miscarriage (defined as three or more pregnancy losses); PPH affected a quarter of the deliveries (half of the PPH occurred in women not on prophylaxis at the time of delivery)[25].

Sex-specific bleeding in Factor X deficiency

Factor X deficiency is one of the most severe inherited coagulation defects, with the onset at an early age with umbilical cord bleeding, CNS hemorrhages, gastrointestinal bleeding, muscle hematomas and hemarthroses[1].

During pregnancy, in healthy women, the level of Factor X increases progressively reaching a first peak at about the 30th week and a second peak of activity on the 6th day after delivery, subsequently returning to pre-conceptional levels in about six weeks. These variations also occur in women with mild or moderate deficiency, but not in those with severe deficiency[27].

Factor X deficiency is associated with abortion, premature birth and peripartum hemorrhage. A recent review analyzing 31 pregnancies in 19 patients with this deficit showed miscarriages in 13%, a proportion that does not seem to be higher than in the general population, although the number of reported pregnancies is too small to allow conclusions, PPH in 22%, and preterm delivery in 30% of successful pregnancies[28,29]. Recently a plasma-derived concentrate of Factor X has been developed for prophylaxis and on-demand treatment, showing good efficacy and safety[30].

Sex-specific bleeding in Factor V deficiency

The hemorrhagic symptoms of Factor V deficiency are poorly correlated with the level of residual factor, and are represented by epistaxis, HMB and oral, mucocutaneous and post-operative bleeding. Muscle hematomas and hemarthroses are also described, as well as spontaneous hemorrhages of the CNS[1,17]. According to a review published in 2013, HBM affects about a third of patients with Factor V deficiency[31]. A concentrate for Factor V deficiency is not currently available for clinical use. The standard treatment remains FFP and, in select cases, platelet transfusions, as Factor V is present in both plasma and platelet α-granules[32]. A novel plasma-derived Factor V concentrate has demonstrated

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efficacy *in vitro* for correcting coagulation parameters in severe Factor V deficiency: it has not yet reached clinical practice or regulatory approval, and its use remains investigational[33].

Sex-specific bleeding in fibrinogen deficiency

Hereditary fibrinogen disorders can be classified based on a complete or incomplete quantitative defect (afibrinogenemia and hypofibrinogenemia, respectively), or based on a functional alteration of the molecule, with or without a quantitative deficiency (dysfibrinogenemia or hypodysfibrinogenemia). The diagnosis of hereditary fibrinogen disorders should include first and second level tests[34]. In afibrinogenemia aPTT and PT are indefinitely prolonged, in hypofibrinogenemia they are prolonged according to fibrinogen level, whereas in functional fibrinogen disorders they are variably prolonged. As a second step, both fibrinogen activity and antigen should be measured. Fibrinogen activity is measured by the Clauss method or the PT (PT-derived fibrinogen). Several immunological assays are available to assess the fibrinogen antigen. In afibrinogenemia activity and antigen levels are undetectable while in hypofibrinogenemia there is a proportional decrease of both activity and antigen. Dysfibrinogenemia is characterized by a discrepancy between a normal antigen fibrinogen level and decreased activity. Hypodysfibrinogenemia is characterized by a discrepancy between decreased antigen and functional fibrinogen. Patients with afibrinogenemia may experience severe bleeding symptoms from childhood: mucocutaneous bleeding, soft tissue bleeding, hemarthrosis, and umbilical cord bleeding[1]; central nervous system hemorrhages are not uncommon, as well as postoperative bleeding in the absence of prophylaxis. Hypofibrinogenemia, defined as values greater than 50-100 mg/dL, is generally asymptomatic, but patients may have an increased tendency to bleed following trauma or surgery[35]. Patients with dysfibrinogenemia are at increased risk of thrombosis, with deep vein thrombosis and pulmonary embolism potentially occurring at a young age[35]; in these patients major bleeds can occur but are more often related to injury, delivery, or surgery[17]. In a review of 250 patients with dysfibrinogenaemia, 26% had bleeding (mucocutaneous, traumatic or surgical)[36]. Reports of venous thromboembolism are also observed cases of afibrinogenemia[1]. The pathophysiology of thromboembolism in hereditary fibrinogen disorders is complex including several mechanisms[37]: impaired thrombin binding (i.e., high level of circulating thrombin due to its impaired clearance by the abnormal fibrinogen) and sequestering (i.e., increased levels of prothrombin activation fragments or thrombin-antithrombin complexes), abnormal fibrin clot structure, mainly due to impaired fibrinolysis caused by the absence on abnormal fibrinogen of profibrinolytic protein binding sites, platelet aggregation via von Willebrand Factor (vWF). In fact, in the absence of fibrinogen, vWF may interact with the platelet glycoprotein IIb/IIIa and could potentially be an alternative mediator of platelet aggregation.

HMB is common in women with afibrinogenemia. In an Iranian study[38], it was present in 70% of patients and was defined as menstrual periods lasting >6 days and requiring treatment such as antifibrinolytics, replacement therapy, hormonal therapy or iron supplementation. There are also reports on reduced fertility in these women[39]. It appears that fibrinogen plays an important role in maintaining pregnancy, ensuring normal fetal circulation development and facilitating embryo implantation: the early pregnancy loss observed in mouse models[40] of fibrinogen deficiency is confirmed by the increased incidence of miscarriage at weeks 5-8 of gestation in women with afibrinogenemia[35,38-40].

Sex-specific bleeding in prothrombin deficiency

Factor II deficiencies are more frequently qualitative (dysprothrombinemia) than quantitative (hypoprothrombinemia). In severe deficiencies there are often mucocutaneous bleeding, muscle hematomas, hemarthroses and gynecological bleeding; moderate or mild forms may be asymptomatic[1,17].

In a study on 14 Iranian women HMB affected 75% of patients, although not in a severe form, while no PPH was recorded[29].

Sex-specific bleeding in combined Factors V and VIII deficiency

This rare defect is caused by genetic mutations of lectin mannose-binding protein (LMAN1) or multiple coagulation factor deficiency genes (*MCFD2*), which encodes proteins involved in the intracellular transport of Factors V and VIII: LMAN1 and MCFD2 form a protein complex that functions as a cargo receptor from

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the endoplasmic reticulum to the Golgi[41]. Combined Factors V and VIII defect is characterized by a mild or moderate bleeding tendency, mostly mucocutaneous and post-operative, whereas HMB is the most common bleeding reported in this subset of women[42,43]. During pregnancy, Factor V level remains stable, whereas Factor VIII increases progressively. Indeed, Factor VIII levels are considered sufficient to ensure proper hemostasis during delivery. A review found abnormal post-partum bleeding in 32% of the deliveries[44].

Sex-specific bleeding in vitamin-K-dependent factors deficiency

This rare deficiency, reported in less than 50 families worldwide, is characterized by levels of Factors II, VII, IX, X, protein C and protein S between 1% and 20%. The synthesis of the enzymatically active form of vitamin K-dependent factors requires the activity of the hepatic γ-glutamyl carboxylase (GGCX) and its cofactor, vitamin K hydroquinone (KH2). During the reaction, KH2 is converted to vitamin K epoxide (KO), which is recycled to KH2 by the vitamin K epoxide reductase 1 (VKOR1) enzyme. Mutations in *GGCX* or the *VKOR* complex genes result in a combined deficiency of vitamin K-dependent coagulation factors[43]. In the newborn it presents with umbilical cord bleeding or CNS hemorrhage (similar to hemorrhagic disease of the newborn resulting from acquired vitamin K deficiency). Children with severe deficiency may present, in association, skeletal abnormalities and hearing defects[1,17]. Persistent HMB and PPH have been described[45]. There is no close correlation between clinical phenotype and the activities of FII, FVII, FIX and FX[36]. Despite decreased proteins S and C levels, there are no reports of venous or arterial thrombosis[43].

Pregnancy and delivery in patients with RBDs

All patients with rare coagulation deficiencies should be offered genetic counseling in the pre-conceptional period, and should be adequately informed about the risk of bleeding during pregnancy and peri-partum; multidisciplinary management is necessary, involving the hematologist, the anesthetist, the gynecologist/obstetrician, the neonatologist, because of the possibility that the newborn has inherited the coagulation defect (theoretically, there is a 50% probability)[46]. Specific factor concentrates are available for treatment and prevention of hemorrhages, and to ensure safe hemostasis at the time of delivery or if invasive procedures are necessary. For deficiencies in which specific concentrates are not available, FFP is used choosing preferably plasma subjected to solvent-detergent treatment for viral inactivation, and in case of fibrinogen and Factor XIII deficiencies, cryoprecipitate[22].

Prophylaxis during pregnancy is recommended in the case of Factor XIII deficiency: due to the high risk of miscarriage, it is reccomended to maintain levels >10-20% in the first two trimesters and >30%, whereas for fibrinogen deficiency a target trough fibrinogen level of ≥1 g/L throughout the pregnancy and ≥1.5 g/L in case of vaginal bleeding is reccomended[47].

Antifibrinolytics are indicated to reduce the risk of PPH, regardless of the type of deficiency[48]. **Table III** summarizes the main guidelines and reviews regarding the minimum hemostatic level for each factor to ensure safe hemostasis, the preferable level for delivery, the half-life of the deficient factor and the suggested treatment[43,48-51].

INHERITED PLATELET DISORDERS

Clinical features and sex-specific bleeding in Inherited Platelets Disorders

Bernard Soulier syndrome (BSS) is due to a complete quantitative deficiency in the GPIb-V-IX complex (vWF receptor); this functional defect of platelet adhesion is associated with thrombocytopenia and a morphological alteration resulting in giant platelets (macrothrombocytopenia)[52]. BSS is caused by *GP1BA*, *GP1BB* or *GP9* gene variants; while most BSS cases show autosomal recessive inheritance, monoallelic forms have been reported. The incidence of BSS is estimated at 1:1.000.000 and the syndrome is characterized by a severe hemorrhagic phenotype with mucocutaneous bleeding, including spontaneous bruising and excessive trauma-induced bleeding[53]. Glanzmann thrombasthenia (GT) is a disorder of platelet aggregation due to defects in the platelet fibrinogen receptor GPIIb/IIIa (CD41/CD61), that can be absent (type I), reduced (type II) or dysfunctional (type III). GT is an autosomal recessive disorder caused by gene variants of *ITGA2B* or *ITGB3*. Bleeding symptoms can vary from mild to severe. Patients usually present in the first year of life with mucocutaneous (purpura, epistaxis, gum bleeding, HMB) or post-trauma/procedure bleeding; gastrointestinal bleeding is present in 10-20%, intracranial

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Table III - *Recommendations for pregnancy and delivery in rare inherited bleeding disorders*[43,48,50,51,71,72]

Deficient factor	Half-life	Hemostatic level	Level of factor required for delivery	Treatment	Reference
Fibrinogen	2-4 days	50 mg/dL	150 mg/dL for 3 days	Pregnancy prophylaxis: fibrinogen concentrate 50-100 mg/kg twice a week to maintain levels above 100 mg/dL delivery: fibrinogen concentrate 50-100 mg/kg; TA; thromboprophylaxis in women with a personal or family history of thrombosis (especially dysfibrinogenemia)	17, 43
Prothrombin	3-4 days	20%	20-40% for 3 days	Prothrombin complex concentrate 20-40 IU/kg; TA	17, 43
Factor V	36 hours	20%	20-40% for 3 days	Fresh frozen plasma 10-15 mL/kg; platelet transfusion	17, 43
Factor VII	4-6 hours	20%	20% for 3 days (5 days for caesarean delivery)	Recombinant activated Factor VII 15-30 mcg/kg; TA	28, 35, 13
Factor X	40-60 hours	30%	40% for 3 days	Prothrombin complex concentrate 10-20 IU/kg	17, 43
Factor XI	50 hours	poor correlation between level and bleeding tendency		Fresh frozen plasma 10-15 mL/kg; TA	17, 43, 75
Factor XIII	9-12 days	30%	not applicable	Plasma factor XIII 20-40 U/kg, recombinant factor XIII 35 U/kg	17, 43
Factors V + VIII	36 hours F. V 12 hours F. VIII	20% F. V 50% F. VIII	20% F. V 50% F. VIII	Fresh frozen plasma 10-15 mL/kg, recombinant factor VIII concentrate	17, 41

TA: tranexamic acid.

hemorrhage in 1-2%[54]. The diagnosis of IPDs is often challenging. First, physical examination and collection of family and personal history are needed. The ISTH-BAT (International Society of Thrombosis and Haemostasis Bleeding Assessment Tool) score is then calculated. This score has been demonstrated to efficiently discriminate IPD subjects, and it has a predictive value for bleeding events at follow-up[55]. Laboratory tests requested for IPD diagnosis are summarized in **Table IV**.

The bleeding tendency in patients suffering from

Table IV - *Laboratory tests for the diagnosis of Inherited Platelet Disorders*[73-75]

First level	
Complete blood count	Platelet count, mean platelet volume and immature platelet fraction (IPF) should be determined
Blood smear examination	Morphological assessment of platelets
PT, aPTT, vWF (antigen and activity)	Exclusion of major defects of primary hemostasis and coagulation
POC (point of care) methods	Platelet function analyzer: automated *in vitro* bleeding time system; it is very sensitive to changes in hematocrit, platelet count, medications (e.g., non-steroidal anti-inflammatory drugs), diet; good sensitivity, poor specificity; lack of standardization
Light transmission aggregometry (LTA) according to Born	Gold standard for moderate and severe IPFD, with specific impact on GT and BSS diagnosis; limitations: moderate-severe thrombocytopenia, hemolytic and lipidemic plasma samples, sensitive to sample handling and intra-analytical variables.
Flow cytometry (FCM) (basic panel)	Useful to study: surface platelet glycoprotein deficiencies; platelet aggregation or secretion; platelet procoagulant function. If platelet aggregation tests do not allow a final diagnosis, FCM is recommended to specify the diagnosis. Advantages: small amount of blood requested (feasible also for pediatric patients), reliability even in presence of thrombocytopenia; weak points: restricted availability, relatively time-consuming, moderate susceptibility to sample handling and preanalytical variables
Second level	
Lumiaggregometry or measurement of ATP release by high-performance liquid chromatography (HPLC)	Bioluminescent method that assesses platelet delta-granule ATP release, typically at the same time as performing LTA
Flow cytometry (extended)	Performing FCM with an extended panel of platelet surface proteins, e.g. to detect some aspects of platelet activation (CD62P, CD40L, CD63)
Third level	
Genetic studies (e.g. next-generation sequencing,, NGS)	Targeted for a gene panel or whole-genome/exome sequencing
Electron microscopy	Visualization of many platelet structures with a resolution of 0.2 nm; indicated to quantify granules release
ELISA for soluble proteins and mediators released from activated platelets	Serum CD62P, serum GPIIb/IIIa, serum GPVI, thromboxane B2, serotonin

PT: prothrombin time; aPTT: activated partial thromboplastin time; vWF: von Willebrand Factor; GT: Glanzmann thrombasthenia; BSS: Bernard-Soulier syndrome; CD: cluster of differentiation; GP: glycoprotein; ELISA: enzyme-linked immunosorbent assay.

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IPDs can be of variable intensity, usually presenting with mucocutaneous bleeding including nosebleeds, ecchymoses, oral bleeding, HMB but also bleeding from minor wounds or following surgery or childbirth. Muscle hematomas, CNS hemorrhages, hematuria and gastrointestinal bleeding may also occur[56]. Moreover, like any other inherited hemorrhagic syndromes, women are more frequently diagnosed with IPD because of menstruation, childbirth, uterine fibroids, endometrial hyperplasia and polyps[57]. Furthermore, even in the mildest forms, IPD can be associated with significant morbidity, especially due to the complications of HMB, such as iron-deficiency anemia, which is significantly associated with a reduction in quality of life[57].

HBM has a reported prevalence of 51% in BSS, and of 98% in GT[58]. In a study analyzing 232 women of childbearing age studied for HMB, 59% had an abnormality of platelet ATP release[59]. In two studies enrolling adolescents with HMB, abnormalities of platelet aggregation were found in 7% and 31% of patients, respectively[58,59]. Initial treatment of HMB involves the use of antifibrinolytics, such as tranexamic acid (TA), started at the beginning of the menstrual flow, with a dosage of 15-25 mg/kg orally three times a day for three days[60]. The second line of therapy consists of the use of Desmopressin (DDAVP), alone or in combination with antifibrinolytics: severe forms of IPD may not respond even with this combined approach[61]. In patients with GT the use of recombinant activated Factor VII has been shown to be effective and safe[60,62]. In those situations in which the above-mentioned measures fail to control menstrual bleeding, hormonal therapy (combined oral contraceptives or progestins) or platelet transfusions are indicated[57]. Furthermore, there are other therapeutic options that include uterine tamponade, endometrial ablation, uterine artery embolization and, in *extrema ratio*, hysterectomy[56].

Regarding pregnancy, there are few data on the frequency of PPH: some authors described a high prevalence of PPH (26 PPH out of 74 pregnancies) in women suffering from GT, while a review analyzing women with BBS reported 18 PPH in 30 deliveries[63,64]. A recent retrospective study on 65 pregnancies in 34 women with IPD showed a PPH frequency of 14% in patients with "storage pool disease" and of 50% in patients with GT[63]. In a systematic review, antenatal bleeding and PPH were reported in about 50% and 30% of patients with GT, respectively, and maternal alloimmunization against platelet antigens was reported in a significant number of pregnancies and it was associated with neonatal death[65].

Pregnancy and delivery in patients with IPDs

Delivery is very challenging for patients affected by IPDs with a high risk of bleeding, which requires a multidisciplinary approach by a team involving a hematologist with expertise in hemostasis, a gynecologist, an anesthesiologist and a neonatologist in order to set up an individualized program of prophylaxis and, if necessary, treatment of PPH[56]. The latter can complicate both vaginal and cesarean delivery[56]. Furthermore, there is no clear recommendation regarding the choice of one or the other delivery method. The newborn, potentially carrying the platelet defect inherited from the mother, must undergo the least possible traumatic stress, therefore extraction with forceps or ventouse is contraindicated[61]. The use of platelet transfusions has a role in the prevention of PPH that is not yet well understood: two large retrospective studies showed a similar incidence of PPH in women who received and those who did not receive transfusions. However, these data may be affected by a selection bias of patients with higher bleeding risk for platelet transfusions, or by an inappropriate dosage[63,66,67]. In the PIPA study, PPH was recorded in approximately half of the women with GT who had received prophylactic platelet transfusions[63]. Further treatments are represented by TA and by activated rFactor VII, which has been used in GT both in prophylaxis and in the emergency treatment of PPH[67].

In BSS, delivery has been adequately managed using prophylactic platelet transfusions and PPH has been treated with TA and DDAVP together with platelet transfusions[56]. In patients refractory to platelet transfusions, antifibrinolytics and activated recombinant Factor VII can be effective[68].

Moreover, oxytocin and prostaglandins, used to increase uterine contractility, essential for hemostasis at delivery, are also recommended. In this case, it is suggested to avoid intramuscular administration, due to the risk of hematomas[56].

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CONCLUSIONS

Women affected by RAIBDs present some peculiar issues that have important implications: HMB is often the most frequent reported symptom, and often the reason for referral[46]. Delayed identification of this type of bleeding can lead to a delay of diagnosis[69]. HMB often provokes iron deficiency, which can be accompanied by anemia and has an important burden in terms of clinical symptoms and quality of life[46]. The rarity of hemostasis defects poses an insidious challenge in the management of pregnancy and delivery, especially if the bleeding disorder is not diagnosed prior to the physiological changes in hemostasis related to these events, which make the diagnosis more difficult. The Italian health system implements in many regions the systematic use of a pregnancy diary in which diagnostic tests are prescribed according to gestational age. However, given the diagnostic delays that have been mentioned, and the fact that HMB can manifest itself as early as adolescence, it would probably be advisable to study hemostasis in adolescence when a suspected hemostasis disorder, in a hemorrhagic phenotype, can be observed. The hemorrhagic phenotype can be systematically quantified with questionnaires such as the ISTH-BAT score[70].

Currently, there is only limited evidence about how to manage patients affected by RAIBDs during pregnancy and delivery, therefore the current clinical practice is often based on local policy. In our opinion, specific open issues that need further studies are: 1) the possible usage of plasma-derived FVII concentrate instead of rFVIIa in the setting of pregnancy[18] (because of its reduced thrombotic risk); 2) the appropriateness of platelet transfusion in IPDs (in particular in GT) due to the risk of alloimmunization and its possible relationship with adverse fetal outcome[65].

In conclusion, women suffering from RAIBDs form a particular population, with great clinical and socio-economic resonance. Further studies including women in RAIBDs registries and clinical trials are necessary to develop guidelines able to guide the physician to treat this subset of patients. Management of women with RAIBDs might be coordinated by a dedicated Hemostasis and Thrombosis specialist embedded within the hospital's Patient Blood Management program; this expert brings unique clinical and laboratory insights to guide individualized hemostatic treatments and ensure judicious use of blood products. Integration of this role fosters multidisciplinary collaboration among hematologists, gynecologists, and anesthesiologists.

Authorship contribution

TM, BB, DP, IR and RA wrote the manuscript. All Authors reviewed and approved the final version of this manuscript.

The Authors declare no conflicts of interest.

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