Gynecologic and obstetric management of girls and women with von Willebrand disease

Rezan Abdul-Kadir[1] and Margaret V. Ragni[2]

[1]The Royal Free NHS Foundation Hospital Institute for Women's Health, University College of London, London, UK and [2]Department of Medicine, Division of Classical Hematology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Correspondence: M.V. Ragni
ragni@pitt.edu

Received: March 4, 2025.
Accepted: April 17, 2025.

https://doi.org/10.3324/haematol.2024.286059

Abstract

Among the first patients with von Willebrand disease (VWD) described by Eric von Willebrand almost a century ago were young girls and women from a family in the Åland Islands who experienced "genital hemorrhage" so excessive that it led to exsanguination in five members.[1] Only recently has attention focused on the risks and challenges that females with VWD face when experiencing heavy menstrual bleeding, conception, pregnancy, and delivery. The persistent monthly losses with heavy menstrual bleeding and increased demands during pregnancy commonly result in iron deficiency, but the lack of consensus regarding screening and treatment leads to underdiagnosis and undertreatment. While the genetics of VWD are known, female members of affected kindreds are infrequently screened and not considered at risk. Among girls and women with VWD in whom reproductive tract bleeding is the most common symptom, a diagnosis of VWD is often delayed up to a decade or more, leading to significant morbidity, fatigue, depression, iron deficiency, and poor quality of life. Furthermore, there is low certainty regarding effectiveness of current therapies and a lack of prospective trials to guide treatment. Novel therapeutics for inherited bleeding disorders are on the horizon, but women are excluded from studies and have poor access to care. While collaborative hematology-gynecology clinics have improved outcomes, females continue to be excluded from decision-making about their own care. Now, 100 years after the first cases of VWD were reported, it is timely to advocate for better care and management of females with reproductive tract bleeding to assure their future well-being.

Gynecologic considerations

Heavy menstrual bleeding

As the first studies of women with von Willebrand disease (VWD) were published, the scope and burden of heavy menstrual bleeding (HMB) began to be realized.[2,3] Although HMB is typically the first symptom of VWD, diagnosis was often delayed up to a decade or more later.[2] With unabated monthly blood loss, fatigue and anemia were common although unrecognized by healthcare providers, and 25% of these women underwent hysterectomies at a median age of 34 years to control bleeding. However, it was not until the women developed postoperative bleeding requiring transfusion that a diagnosis of VWD was considered, typically precipitated by a call to a hematologist to help manage their postoperative bleeding.[2] Unlike women without a bleeding disorder, they had bleeding that lasted for weeks or months beyond the postoperative period.[2] Only then was the bleeding and family history obtained and VWD tests performed, confirming a diagnosis of VWD, and treatment was prescribed to stop the acute bleeding. As these women with HMB became patients at the local hemophilia centers, experience grew in their care and as did proactive collaboration of hematologists and gynecologists and surgeons, who screened for VWD before surgery, leading to a reduction in postoperative bleeding.

Definition and scoring systems for heavy menstrual bleeding

With the growing understanding of hemostasis and the function of von Willebrand factor (VWF) in facilitating interactions between platelets and the vascular endothelium to form the platelet plug (primary hemostasis) and with other factors to form a fibrin clot (secondary hemostasis), so too was the critical function of VWF in ensuring hemostasis and reducing HMB in VWD recognized. HMB

is quantified as >80 cc blood loss per month, a level at which progressive iron loss and iron deficiency commonly occur.[4] A minimal workup for HMB should include a menstrual history, family history, and bleeding history to assess for the presence of a bleeding disorder, along with a complete clinical blood count, measurement of ferritin levels, and a standard gynecologic examination to assess for other causes of bleeding, e.g. fibroids, polyps, cancer, ovarian disease, or other anatomic disorders.[5,6]

Assessment of the severity of heavy menstrual bleeding

Scoring systems[7,8] and standardized tools were developed to measure HMB.[8-11] Although the original test to measure HMB was by alkaline hematin spectrophotometry of pads and tampons collected during the menstrual period,[4] it was impractical in clinical practice and replaced by the pictorial blood assessment chart (PBAC).[9] The PBAC quantifies menstrual severity in a single score by summing the number and degree of pad or tampon saturation during a cycle, with 1, 5, and 10 points for mild, medium, and severe saturation of tampons, and 1, 5, and 20 points for pads. A PBAC score of 100 correlates with >80 cc blood loss with r=0.85, and 86% sensitivity and 89% specificity.[12] The PBAC is a practical measure of HMB and the current "gold standard." Widely used by patients, commonly as an online application, and by experts in practice and in clinical trials, the PBAC is a subjective tool with high variability, potentially limiting its validity.

Three predictors of HMB identified in regression analysis from a study of 161 patients include (i) clots >1 inch in diameter, (ii) low serum ferritin, and (iii) changing pads or tampons hourly.[13] Together these variables predict HMB with 60% sensitivity and 86% specificity. Other factors may refine HMB risk, including bleeding history, cycle length, "flooding", family history, and surgical history, which showed 82% sensitivity for HMB; however, when combined with the PBAC, their sensitivity for HMB increased to 95%.[14] HMB has also been measured by the International Society of Thrombosis and Haemostasis (ISTH) Blood Assessment Tool (BAT),[15] a sensitive and specific tool to screen for general bleeding symptoms in VWD, a subset of which screens for HMB in women with VWD. While the ISTH BAT is more sensitive than the PBAC score for measuring HMB, it is limited by variability in thresholds by age, so age adjustment is required.[16] An elevated BAT score, however, is considered best used as a support for the identification of a bleeding disorder to prompt testing for VWD,[5] although in adolescents and young women, HMB may be the only bleeding symptom, and should prompt clinicians to test for VWD even if the BAT cutoff score is not reached.[17]

The inconsistency and complexity of HMB measurements by some tools has led to the proposal that simpler definitions be adopted that focus on the impact of HMB on a woman's health. The UK National Institute for Health and Care Excellence (NICE) defines HMB as excessive blood loss that interferes with a woman's physical, emotional, and social well-being and quality of life.[18] The American Society of Hematology (ASH) proposes a definition that facilitates consistency for future comparisons of studies or treatment, defining HMB by any of the following criteria: bleeding lasting 8 or more days, associated with passing blood clots, soaking through one or more pads or tampons every 2 hours on multiple days, or requiring change overnight, or a PBAC score over 100.[19] While consistency of definition is necessary, consensus on the definition of HMB remains elusive.

Screening for von Willebrand disease in women with heavy menstrual bleeding

Despite the high prevalence and heavy burden of HMB, only 8% of adolescent females with HMB are screened for VWD.[15] Those who are screened are more likely to have an affected family member or receive care at a hemophilia treatment center (HTC).[20] Yet, gaining access to care at an HTC requires breaking down barriers,[20] welcoming females to receive care,[21] taking family histories and encouraging genetic studies,[6,22,23] incorporating female perspectives into care[24] and decision-making,[25,26] and including females in registries for prospective data collection[25] and clinical trials[21,27,28] (Table 1). In addition, patient education and provider training are critical to the recognition and management of HMB.[29,30] Importantly, many HTC have incorporated a multidisciplinary team including hematologists and gynecologists to coordinate and improve care for women with bleeding disorders.[5,25,31]

Table 1. Clinical burden of bleeding disorders in women with von Willebrand disease.

Problems	References
Delay in diagnosis: lack of recognition of HMB by patients and providers	29, 30
Lack of screening for iron deficiency, although highly prevalent	36, 40
Lack of definitive treatment, monitoring for iron deficiency	36, 39, 40, 44
Cognitive, physical, and psychosocial defects in iron deficiency	32-34, 36, 41, 49
Depression, poor quality of life	29, 47, 48
Lack of effective therapies to prevent and treat HMB and PPH	43, 56
Lack of inclusion of females in decision-making regarding their own care	24, 26
Insufficient evidence for guidelines for treatment	43
Lack of guidelines for iron deficiency management	34 ,41, 44
Lack of inclusion of women in VWD clinical trials	21, 27
Difficulty of conducting rare disease clinical trials	26
Lack of consistent outcome data, including patient-related outcomes	28, 117

HMB: heavy menstrual bleeding; PPH: postpartum hemorrhage; VWD: von Willebrand disease.

Iron deficiency and iron deficiency anemia

As a result of heavy monthly blood loss, iron stores may be depleted in at least 60% of adolescents and women with HMB have iron deficiency, whether defined as ferritin <15 ng/mL[32] or <30 ng/mL.[5] The degree of iron deficiency correlates not only with the severity of blood loss, but also with impaired cognitive, physical, and psychological functioning, and poor quality of life[32-35] (Table 1). Once identified, however, these symptoms are reversible with iron replacement,[34] but there remains a significant gap in diagnosing iron deficiency in these adolescents and adult females. Despite the high frequency of iron deficiency and iron deficiency anemia, very few adolescents and women with VWD are screened.[36] In the Iron Ladies Study HTC survey, 70% of 142 providers participating in the American Thrombosis Hemostasis Network (ATHN)[27] reported that they routinely screened for iron deficiency in females of reproductive age with inherited bleeding disorders (54% with VWD). Yet, among 10,527 females seen between 2015 and 2019 within ATHN-affiliated HTC, only 3.6% were tested for iron deficiency, 71.9% of whom were found to be iron deficient.[27] These findings highlight the significant gap in identifying iron deficiency in females of reproductive age, and, importantly, providing iron replacement. Thus, iron deficiency is underdiagnosed, patient morbidity persists, and the precise incidence and prevalence remain unknown.

Iron replacement therapy

Not only are there gaps in screening for iron deficiency in women with VWD and HMB, the treatment of iron deficiency is also suboptimal. While oral iron is effective in reversing symptoms, it may be poorly tolerated with nausea and/or constipation, resulting in poor compliance. Although the optimal dose is not known, a randomized trial showed improved iron absorption with every-other-day dosing.[37] For women and girls with HMB who are intolerant or unresponsive after one or two cycles, intravenous iron can be instituted, with a more rapid increase in hemoglobin and few side effects.[35] Response to treatment may be monitored by assessing the PBAC, ferritin and hemoglobin levels, and quality-of-life tools such as the Short Form 36 (SF-36), but the approach is not standardized. Moreover, despite the effectiveness of iron replacement, long-term follow-up indicates fewer than half of females treated for iron deficiency experience resolution up to 3 years later.[38] Although iron deficiency continues to be a major public health problem in women with HMB,[39,40] clinical evidence is limited and established cutoffs for iron and ferritin levels are lacking. As a result, no official recommendations for iron deficiency screening or treatment exist.[34] In a review of clinical guidelines on the management of women with HMB for anemia,[41] of 16 identified, 11 offered no recommendations on screening, four recommended against screening, and only eight recommended iron replacement, four each with oral and intravenous therapy. The American College of Obstetrics and Gynecology (ACOG) recommends a complete blood count and serum ferritin level to screen women with HMB for iron deficiency[38,42] and the ASH suggests annual monitoring of women with bleeding disorders and HMB.[43] With no consistent evidence-based approach to screening and treatment, the deliberations of a recently formed ASH task force to determine practice guidelines for the management of iron deficiency are eagerly awaited.[44] In summary, to address and improve gaps in iron deficiency care, definitions of iron deficiency should be harmonized, reproductive-age females should be routinely screened, evidence-based iron replacement regimens implemented, provider education improved, and iron deficiency and HMB databases maintained to provide evidence-based research.[24]

Quality of life

In addition to the burden of iron deficiency, women with VWD and HMB have poor quality of life, with fatigue, pain, and depression which affect family life, physical health, psychological health, and social life.[15,45,46] In addition, HMB has socioeconomic consequences, including days lost at work, depression, and high healthcare costs.[32,33,45,47-49] In one of the first studies of HMB in women with VWD,[4] significant morbidity was associated with gaps in health care, including delay in diagnosis, failure to obtain a preoperative bleeding history to prevent postoperative bleeding, and lack of recognition that bleeding disorders occur in women or that HMB could be part of an underlying bleeding disorder. While 25% of this cohort underwent hysterectomy at a median of 34 years of age and 13% experienced postpartum bleeding, the majority of women in this study considered HMB 'normal' in their family. These findings underscore the public health importance of obtaining a personal and family bleeding history in women with HMB and the importance of early recognition, testing, and intervention.[9,50]

The impact of HMB on quality of life is most commonly assessed by the SF-36,[45,49,51] which has confirmed the greater impact of HMB on health and well-being, with poorer SF-36 scores in women with bleeding disorders than in women with normal hemostasis.[45] HMB affects family life, physical health, work life, psychological health, and social life,[47] and is associated with anxiety, depression, and barriers to care, contributing to poor quality of life,[32,41,48] further reduced by lack of effective therapies for HMB.[15,20,46,47,49,51] To achieve equitable health for women with HMB, accurate diagnosis, access to multidisciplinary care,[5,25,31,52] and provider and patient education[9,30] are needed. Prospective data collection through registries that include women,[25] family genetics and genomics research[6,22,23] should be encouraged, as should patients' participation in the design and conduct of VWD research.[26]

Treatment of heavy menstrual bleeding in women with von Willebrand disease

The lack of safe, effective treatment for HMB in women with VWD is a persistent public health problem,[39] with

few randomized trials available to guide treatment and condition international guidelines regarding hormonal and non-hormonal agents.[43] Therapeutic options available to treat HMB include hormonal, hemostatic, surgical or non-factor agents, and there are a number of novel non-factor hemostatic therapies in development (Table 2). Yet, the choice of therapy requires the development of an HMB treatment plan. This plan is centered on the patient, her preferences, lived experience, and reproductive plans.[21,25,43] Decisions should be made within a supportive, collaborative multidisciplinary team that includes a gynecologist and a hematologist.[5,25,31,52] Factors that may affect a woman's decision regarding HMB treatment include the severity of her VWD, fertility plans, requirement for contraception, underlying gynecologic disease, and potential side effects of treatment, as well as potential risk factors, including age, body mass index, diabetes, hypertension, polycystic ovary disease, and endometrial hyperplasia or malignancy.[43]

How does the type and severity of VWD impact decision-making? Importantly, the severity of the woman's VWD and current treatment for non-HMB bleeds are critical in therapeutic decision-making. While no specific guidelines exist, there are some practical approaches. If a patient has mild or moderate disease and is not receiving any routine therapy, first-line drugs might include hormonal products, antifibrinolytic agents, or hemostatic agents. By contrast, if a patient has severe disease (e.g. type 2 or type 3 VWD) and is already receiving a hemostatic agent for non-HMB bleeds, then changes in the dose or type of current hemostatic agent, e.g., a clotting factor concentrate, or addition of an antifibrinolytic agent, or a hormonal agent might be considered. The future use of off-label hemostatic or novel non-factor agents currently in preclinical studies or clinical trials (Table 2) will require the same careful assessment of the patients before an agent is added to a treatment plan. Finally, after the initiation of any therapeutic agent, response to treatment should be assessed including by the PBAC, ferritin and hemoglobin levels, and quality of life.[53]

Table 2. Therapeutic approaches to reduce heavy menstrual bleeding in females with von Willebrand disease.

Therapeutic approaches	Mechanism of reducing HMB	Type of VWD	Route of administration
Current approaches			
DDAVP[58,59]	Releases VWF from endothelium, increases VWF and FVIII	Type 1, 2	IV, SC, IN
Tranexamic acid[60,63]	Inhibits fibrinolysis	Type 1, 2, 3	IV, PO
Combined oral contraceptive[54]	Increases FVIII and VWF synthesis	Type 1, 2, 3	PO
Levonorgestrel intrauterine system[56,57]	Releases local progesterone into the uterine cavity	Type 1, 2, 3	IU
Plasma-derived VWF[61]	Increases VWF exogenously	Type 1, 2, 3	IV
Recombinant VWF[62,63]	Increases VWF exogenously	Type 1, 2, 3	IV
Endometrial ablation[5,50,64]	Removes endometrium by curettage, radiofrequency or microwave energy	Type 1, 2, 3	-
Hysterectomy[6,65]	Removes uterus	Type 1, 2, 3	-
Novel approaches			
Efanesoctocog[67,68]	Fusion protein FVIII-Fc-VWF-XTEN, increases FVIII exogenously	Type 2N	IV
Emicizumab[69-71]	Bispecific monoclonal antibody, mimics FVIII	Type 2, 3	SC
Rondaraptivon pegol BT200[72,73]	Aptamer blocks VWF-binding LRP1, increases VWF half-life	Type 2B	SC
KB-V13A12[74]	Nanobody binds VWF and albumin, increases VWF half-life	Type 2B Preclinical	SC
VGA039[75]	Monoclonal antibody to protein S inhibits TFPI and APC, improves thrombin generation	Preclinical	IV, SC
HMB-011[76]	Bispecific antibody binds FVIIa, prolongs FVIIa half-life	Preclinical	IV
Platelet nanoparticles[77]	Nanoparticle binds VWF, platelets, prolongs VWF half-life	Type 2B, 3 Preclinical	SC
siRNA[78-81]	Allele-specific siRNA	Type 2A, 2B Preclinical	IV
AAV gene therapy[82]	AAV targets endothelium VWF	Preclinical	IV

HMB: heavy menstrual bleeding; VWD: von Willebrand disease. DDAVP: desmopressin; VWF: von Willebrand factor; FVIII: factor VIII; IV: intravenous; SC: subcutaneous; IN: intranasal; PO: *per os*; IU; intra-uterine; LRP1: low-density lipoprotein receptor-related protein 1; TFP1: tissue factor pathway inhibitor; APC: activated protein C; FVIIa: activated factor VII; siRNA: small interfering RNA; AAV: adeno-associated virus.

Current hormonal and hemostatic therapies

Hormonal agents. While treatment of HMB is typically initiated with single-agent therapy, ultimately, most adolescents and women require two or more agents, typically hormonal and hemostatic, to reduce HMB.[43,54] The first agent generally prescribed to reduce HMB is a hormonal agent, either combined hormonal contraception or the levonorgestrel intrauterine system (Table 2).[43] Low-dose formulations of combined hormonal contraception generally prescribed to women with HMB may be insufficient, with mid-level dosing typically required to reduce HMB in women with VWD. The advantages of the levonorgestrel intrauterine system are long-term HMB protection not requiring a daily pill and avoidance of common side effects of combined hormonal agents, e.g. headache, bloating, mood changes and, less commonly, hypertension.[54,55] The UK Haemophilia Centre Doctors' Organisation (UKHCDO) guideline recommends the levonorgestrel intrauterine system as a first-line therapy for all women with bleeding disorders who do not wish to conceive,[5] although the scarcity of data from five case series suggests low certainty regarding the effectiveness of the system compared with other therapies for HMB in women with VWD.[56]

Hemostatic agents. Among hemostatic agents available to treat HMB, an initial approach is the intranasal agent desmopressin (DDAVP) which releases VWF from the vascular endothelium (Table 2).[58,59] While DDVAP can be given intravenously, the intranasal route allows for treatment at home, and when used for 3-5 days of the menstrual cycle, complications including tachyphylaxis and fluid retention are rare, although DDAVP is usually ineffective in type 3 and most cases of type 2 VWD. Tranexamic acid (TXA), an oral antifibrinolytic agent taken three times daily,[60] is preferred over DDAVP as, despite the pill burden, it is more effective in reducing HMB as shown in a randomized trial and observational study.[54,60]

For girls or women intolerant of or unresponsive to hormones, DDAVP, or TXA, intravenous factor replacement therapy may be prescribed. Various clotting factor concentrates, including plasma-derived VWF with different VWF/factor VIII (FVIII) ratios[61,62] and recombinant VWF with no FVIII[62,63] (Table 2), have been shown in clinical trials to safely and effectively reduce bleeding, including HMB, in women with VWD. Their use is limited by the cost and the inconvenience of intravenous infusion. In a randomized, crossover trial of women with mild VWD comparing recombinant VWF and TXA, both agents reduced HMB as measured by the PBAC, but neither agent corrected PBAC to the normal range, and as TXA is less costly, it may be the more cost-effective approach.[63] Future studies are needed to assess these agents in more severe VWD, in combination, and in combination with hormonal agents, given the lack of thrombotic risk when combining hormones and hemostatic agents in clinical practice.[62]

Surgical approaches for heavy menstrual bleeding

For women who have completed childbearing, surgical options include endometrial ablation[5,50,64] and/or hysterectomy.[5,65] Endometrial ablation prevents HMB by removing the endometrial lining of the uterus by heated liquid, radiofrequency, or microwave energy. The procedure is safe and effective in reducing HMB, with a 1% risk of procedural bleeding and up to 5% requiring a repeat procedure.[64,66] In women for whom all other options have failed, hysterectomy may be performed.[5,65] As compared with ablation, hysterectomy has a higher frequency of intra- and postoperative bleeding, 2%, and blood transfusion requirement, 7%.[5] For any surgical procedure in patients with VWD, a hemostatic plan should be written specifying the procedure, bleeding risks, type of anesthesia, planned hemostatic agents and route, and frequency and duration of follow-up.[5]

Off-label use of Food and Drug Administration-approved therapeutics

In addition to the standard Food and Drug Administration (FDA)-approved hemostatic and hormonal agents (Table 2), there is increasing interest in off-label use of FDA-approved factor and non-factor therapies for HMB given their longer half-life, which could allow for once per menstrual cycle dosing (Table 2).

These agents include efanesoctocog alfa, the long-acting fusion protein FVIII-Fc-VWF-XTEN, which decouples the FVIII-VWF interaction to achieve a prolonged half-life of 7 days and is safe and effective in hemophilia A.[67] Its effectiveness in VWD was first reported in a 78-year-old woman with homozygous type 2N VWD and a FVIII level of 0.05 IU/dL undergoing dental extraction.[68] Following intravenous infusion, there was sustained FVIII elevation with no bleeding. The lack of an increase in VWF levels reduces concerns about adverse cardiovascular effects, but future use of efanesoctocog alfa in VWD will require clinical trials and phenotyping potential subjects as it may not be effective in other heterozygous variants or in type 1 VWD.

Another potential approach to reduce HMB is off-label use of emicizumab, the subcutaneous FDA-approved bispecific monoclonal antibody that mimics FVIII, and is safe and effective in preventing bleeds in hemophilia A and B with and without inhibitors.[69] *In vitro* studies have demonstrated that emicizumab improves thrombus formation under shear in all types of VWD.[70] Recently, it was successfully used off-label to treat hemarthroses in type 2 and 3 VWD, and in a young girl with type 3 VWD and HMB refractory to standard therapy and complicated by hypovolemic shock.[71] Clinical trials of emicizumab in patients with VWD are in progress while off-label use continues, underscoring the need for better therapies in this population.

Novel non-factor therapies in development

A number of novel non-factor agents are in preclinical development which may prevent HMB in women with VWD (Table 2).

BT200 is a pegylated aptamer, rondoraptivon pegol, which delays VWF clearance and prolongs the half-life of VWF by binding VWF A1, reducing its interaction with macrophage LRP1.[72] In a phase II trial in type 2B VWD, subcutaneous BT200 was safe and improved VWF and FVIII levels and platelet counts and restored high molecular weight multimers.[73]

KB-V13A12 is a nanobody-based bispecific antibody that increases VWF half-life by simultaneously binding VWF and albumin.[74] In humanized VWD1 mice, subcutaneous administration increased VWF antigen (VWF:Ag) levels for up to 10 days, and restored multimers and hemostasis with these effects being comparable to those achieved by VWF concentrate.[74]

VGA039 is an anti-protein S antibody that inhibits tissue factor pathway inhibitor and activates protein C to improve thrombin generation.[75] When given subcutaneously or intravenously to VWF-deficient mice, thrombin generation was increased in both *in vitro* and *ex vivo* studies.[75]

HMB-001 is a bispecific monoclonal antibody that binds activated factor VII (FVIIa) and targets it to the activated platelet surface, promoting factor X activation and thrombin generation.[76] When administered subcutaneously to monkeys, there was *in vivo* accumulation of FVIIa and, when studied *ex vivo* in Glanzmann's thrombasthenia platelets, HMB-001 improved fibrin formation, suggesting its potential to treat disorders for which FVIIa is effective.

Synthetic platelet liposomal nanoparticles contain surface peptides that bind collagen, VWF, and activated platelets.[77] In tail clip assays in type 2B and type 3 VWD mice, synthetic platelet nanoparticles reduced blood loss to an amount similar to that occurring in wild-type mice.

Small interfering RNA (siRNA) VWF selectively inhibits translation of a specific mutant VWF transcript. In a model of type 2A VWD, after intravenous injection, it improved VWF protein expression and multimerization.[78,79] In a heterozygous 2B mouse model, after intravenous injection multimeric structure normalized and collagen binding and bleeding times improved.[80] Endothelial siRNA delivery via encapsulation in lipid nanoparticles also resulted in allele-specific VWF inhibition.[81]

Adeno-associated virus VWF gene therapy, using an endothelial-specific dual hybrid adeno-associated virus vector, successfully delivered VWF cDNA *in vitro* in human umbilical vein endothelial cells and *in vivo* in VWD mice, resulting in long-term VWF expression.[82]

In summary, these data suggest that, if proven in clinical trials, these novel agents may have therapeutic potential to reduce HMB.

Obstetric considerations

The risk of postpartum hemorrhage (PPH) in VWD has been known since the first description of the disease when Erik von Willebrand described the bleeder family in Åland in 1926; he reported predominance in girls and women due to "genital hemorrhage" in connection with menstruation and delivery. Among the female members in the family, five deaths have occurred due to bleeding. Hjördis, the index case, died during her fourth menstrual period and her maternal grandmother, Mrs. Augusta S, had bled to death in childbirth.[1] However, it is only in recent years that attention has been drawn to the risks and challenges facing women with VWD when planning to conceive and during pregnancy, delivery and the postnatal period. While the risk of PPH is well established in women with VWD, data remain limited on bleeding risks and complications during pregnancy such as miscarriage and antepartum hemorrhage. Similarly, there is a lack of high-quality data to support evidence-based management during pregnancy and delivery. Thus, uncertainties and variations exist in clinical practice when managing pregnant women with VWD. An international survey of 132 healthcare professionals from 39 countries conducted in 2021 through the ISTH identified considerable disparities in maternity care and wide variations in the antenatal, peripartum and postpartum management of women with VWD.[83] To overcome these challenges and address current knowledge gaps, international collaborative research and common data collections are required to provide evidence for improved and equitable maternity care.

Changes in factor VIII and von Willebrand factor levels in pregnancy

Changes in FVIII and VWF levels during pregnancy vary among women with VWD depending on the severity and type/subtype of VWD as well as the underlying genetic mutation. In women with type 1 VWD, there is a progressive pattern of increase in FVIII and VWF during pregnancy[84,85] and most women with mild VWD (baseline VWF and FVIII levels >30 IU/dL) achieve factor levels in the normal range at the end of pregnancy.[84,86] Conversely, those with more severe deficiency (baseline factor levels <20 IU/dL) exhibit a poor hemostatic response to pregnancy because they are more likely to have compound heterozygote VWD genetic alterations or variants causing increased VWF clearance.[86]

In type 2 VWD, there is usually an increase in FVIII and VWF:Ag but no or a minimal increase in VWF activity.[85] In type 2B, thrombocytopenia may develop or worsen during pregnancy due to spontaneous platelet aggregation by increased abnormal VWF multimers. Women with type 3 VWD show no increase in FVIII and VWF levels during pregnancy.[84] Figure 1 demonstrates changes in FVIII and VWF levels in pregnancy. The pregnancy-induced rise in FVIII and VWF starts to decline from day 3 after delivery and factor levels approach baseline within a week, returning to non-pregnant levels by the third week after delivery.[87,88]

Given the heterogeneity of VWD and variability of hemostatic responses to pregnancy, it is recommended that coagulation factors (FVIII, VWF:Ag and VWF:RCo), and platelet

count in women with type 2B VWD, are monitored during pregnancy and at booking, prior to invasive procedures, and repeated at each trimester of pregnancy[89] to identify those who require hemostatic treatment in case of emergencies and during delivery. Monitoring may also be necessary after delivery, especially for women, to determine the extent and duration of hemostatic treatments required.[88,89]

Antenatal bleeding risks and complications

There is a lack of prospective data in the literature on the risk of bleeding during pregnancy, miscarriage (defined as loss of pregnancy before viability, i.e., 24 weeks of gestation) and antepartum hemorrhage (vaginal bleeding from 24 weeks of gestation) in women with VWD. Retrospective cohort studies indicate no difference in miscarriage rate among women with VWD, including those with type 3 severe VWD, compared to the general population.[84,90-92] Similarly, VWD does not appear to be associated with an increased risk of placenta-mediated pregnancy complications.[91,92] A large national database from the United States including 4,067 deliveries in women with VWD found no increase in fetal growth restriction, placental abruption or preterm births compared to those in women without VWD.[93]

Antepartum hemorrhage/bleeding is vaginal bleeding occurring from 24 weeks of pregnancy and prior to delivery. It complicates 3-5% of pregnancies in the general population and is often associated with adverse perinatal and maternal outcomes.[94] An increased risk of antepartum hemorrhage has not been reported in case series of women with VWD.[84,86,95] In a study including 100 women with type 3 VWD who had delivered at least one child with no prophylactic therapy during pregnancy, no bleeding was reported during the antenatal course.[91] However, a case-control study by the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality utilizing the United States Nationwide Inpatient Sample reported antepartum bleeding in 280/4,067 (6.8%) women with VWD, which is 10 times more frequent than in the control group, but with no increase in the risk of placental abruption or other antepartum hemorrhage-associated adverse pregnancy outcomes.[93] It possible that women with VWD are more likely to be admitted to hospital during pregnancy if they experience antepartum hemorrhage, even if the bleeding is mild.

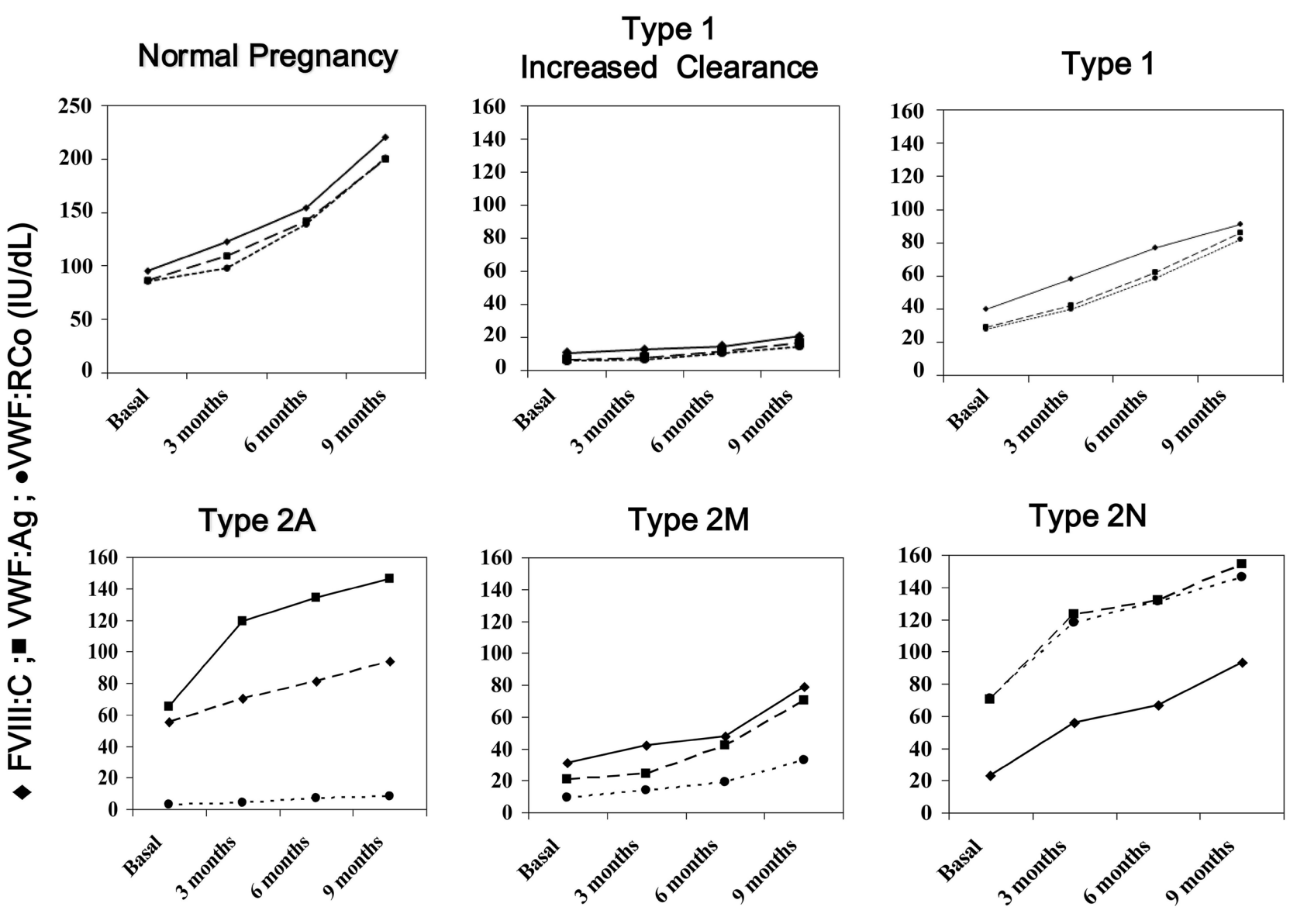

Figure 1. Changes in factor VIII and von Willebrand factor during pregnancy in women with von Willebrand disease. FVIII:C: factor VIII procoagulant activity; VWF:Ag: von Willebrand factor antigen; VWF:RCo: von Willebrand factor ristocetin cofactor. Figure reproduced, with permission, from *the Mediterranean Journal of Hematology and Infectious Diseases*.[86]

Anemia, especially anemia due to iron deficiency, is very common among pregnant women worldwide and associated with adverse maternal and fetal/neonatal outcomes. Women with VWD may enter pregnancy with preexisting iron deficiency or anemia due to their bleeding tendency and longstanding HMB. With increasing iron demand during pregnancy, especially towards the third trimester of pregnancy to meet the demands of the growing fetus, women with VWD are more prone to developing anemia. In the case-control study mentioned above[93] at the time of delivery, women with VWD were twice more likely to be diagnosed with anemia during pregnancy.

Anemia is a significant risk factor for PPH[96] and maternal mortality due to PPH.[95] The risk of death for women with PPH has been reported to be almost 7-fold higher when they are anemic.[97] Therefore, Identification and management of iron deficiency and anemia are important aspects of antenatal care and management of women with VWD.

Peripartum and postpartum bleeding risks and complications

Maternal risks

The main maternal bleeding risk in relation to childbirth is PPH. Women with VWD are at an increased risk of primary PPH (within 24 hours of childbirth) and secondary PPH (from 24 hours to 6 weeks after delivery). Due to inconsistencies in the definition of PPH and lack of objective methods to assess blood loss at delivery, the reported rates of PPH among women with VWD are inconsistent and vary widely among different studies. In a systematic review including 811 deliveries in women with VWD from 71 case reports and series and 16 cohort studies the overall incidence of primary PPH was 34%[98] compared to a rate of 5-8% in the general obstetric population. The study also showed a similar incidence of primary PPH in women who received peripartum prophylactic treatment and those who did not.[98] Women with severe VWD and factor levels (FVIII and VWF:RCo) <50 IU/dL at the end of pregnancy and those with type 2 and 3 VWD are particularly at risk of severe PPH with 5-11% of such women requiring blood transfusion.[84,99] Data from a Dutch retrospective cohort study of women with VWD and carriers of hemophilia from three HTC between 2002 and 2011 reported a 34% rate of PPH and 8% rate of severe PPH (blood loss of 1,000 mL or more) with a higher rate in women who received prophylactic treatment because of low factor levels below <50 IU/dL.[100] More recent Dutch data from six HTC between 2012-2017 showed comparable and stable rates of 28% and 10% for PPH and severe PPH, respectively.[101] Women with factor levels <50 IU/dL and those with type 2 and 3 VWD also had the highest incidence and severity of PPH.[101] Even in women with VWD, the most common causes of PPH are uterine atony, retained placenta/placental tissue, and genital tract trauma. The incidence of PPH is increasing in the general population due the changing obstetric population (e.g., increasing maternal age and obesity) and obstetric practice (increasing rate of induced labor and Cesarean section, etc.) which is culminating in increasing obstetric risk factors, particularly for uterine atony. Although the available evidence on peripartum management in women with VWD remains of low quality, over the years there has been increased awareness and improved joint obstetric and hematology care for the peripartum management of women with VWD. However, there remains room for further improvement, especially for those with severe disease with low factor levels requiring factor replacement therapy to ensure adequate hemostatic factor levels at the time of delivery.

Secondary PPH is excessive bleeding from the birth canal between 24 hours and 12 weeks after delivery. Because pregnancy-induced increases in VWF and FVIII decline after delivery to pre-pregnancy levels within 7-21 days,[88] women with VWD are at an increased risk and typically present around day 6-9 after delivery. In contrast to the 1-2% incidence of secondary PPH in the general population, rates of 12-20% have been reported among women with VWD, of whom 27% needed blood transfusion.[84,102] Women with VWD are also more likely to experience covert bleeding in the form of perineal/vaginal hematomas with any birth canal trauma. In a United States study using hospital discharge codes, women with VWD were three times more likely to have a perineal hematoma compared to women without VWD.[93]

Fetal/neonatal risks

There are increases in VWF and FVIII levels in neonates, induced by the process of labor and delivery.[103] However, neonates with severe VWD may still have reduced VWF and FVIII levels and potentially be at risk of bleeding. Serious bleeding problems are uncommon in infants with VWD, including those with type 3 disease. Data on bleeding risk in relation to the birth process in neonates with VWD are very limited. Among 105 infants and toddlers with VWD <2 years of age, intracranial hemorrhage was reported in 5%; none was associated with delivery.[104] However, extracranial bleeding (cephalohematoma) at birth was reported in 9% of 113 pediatric patients with VWD; half of them were delivered by ventouse extraction and scalp bleeding from invasive monitoring with a fetal scalp electrode was reported in two cases.[105] In another study of 100 children with VWD, cephalohematoma was reported in seven; five (71%) were delivered with the aid of a ventouse cup.[11] There have been no reported data on any bleeding complications with vitamin K administration or immunization.

Management of pregnancy

Antepartum care

A multidisciplinary management approach and collaboration between the obstetric team and the HTC are essential for care of pregnancy in women with VWD.[25] Women with

severe VWD and types 2 and 3 VWD are best managed at a maternity unit affiliated to a HTC with access to laboratory facilities for monitoring VWF and FVIII levels as well as access to hemostatic treatments such as DDAVP and factor concentrate, if required.[25] However, women with mild or moderate type 1 VWD can be safely managed in their local obstetric units with close collaboration with the HTC. In general, women with VWD do not require routine hemostatic treatment prophylactically during pregnancy; however, each woman should be individually assessed and report any bleeding complications. Women with VWD can be exposed to antepartum hemostatic challenges such as miscarriage and invasive prenatal diagnostic procedures. These events mostly occur during the first trimester, typically prior to the pregnancy-induced rise in coagulation factors and can lead to an increased risk of bleeding complications.[84] Assessment of bleeding risk and FVIII and VWF levels should be performed prior to these events to ensure hemostatic support with TXA for those with factor levels >50 IU/dL and DDAVP (in responsive cases) or VWF-containing concentrates for those with factor levels <50 IU/dL.

In the event of obstetric bleeding, assessment by the obstetric/midwifery team should focus on identifying underlying obstetric causes and plan the management accordingly[106] in collaboration with the HTC to determine the need for hemostatic treatment. TXA can be used for women with VWD and bleeding in pregnancy. There are limited data and unfounded concerns on a thrombotic risk from the use of TXA during pregnancy, but reduced duration of bleeding and improved obstetric outcome have been shown with TXA in early pregnancy bleeding without any adverse events (including thromboembolic events) in a small number of studies.[106-108] A clotting factor concentrate, whether plasma-derived or recombinant, may be required when there is heavy or persistent bleeding, especially in women with severe VWD. When there is recurrent vaginal bleeding, subchorionic hematoma or previous recurrent pregnancy losses, prophylactic therapy with VWF-containing clotting factor concentrate should be considered on an individual case basis. The mother should also be counselled on the lack of evidence to support the efficacy of such an approach in improving pregnancy outcome and risks of repeated administration of factor concentrates. The choice of concentrate is based on the type of VWD and local availability but, if appropriate, recombinant factor concentrates are the preferred option in pregnancy.

Women with VWD do not require additional antenatal visits or obstetric monitoring during an uncomplicated pregnancy. Iron deficiency and iron-deficiency anemia are common in women with bleeding disorders and are associated with adverse maternal and neonatal outcomes and are a significant risk factor for PPH.[109] Therefore, hemoglobin level and iron status should be checked and optimized prior to delivery.[89,106] Another important aspect of antenatal care is preparation for delivery through an individualized multidisciplinary team plan for intrapartum and postpartum management. Maternal bleeding risk is assessed based on the type of VWD, third trimester FVIII and VWF:RCo levels and bleeding phenotype. The mother should be counseled about inheritance and the chance of the fetus being affected and the bleeding risk during birth and the neonatal period as well as her risk of PPH. The delivery plan should include a decision on where the delivery should take place (local maternity unit or tertiary center), mode of delivery, pain relief and anesthesia, as well as obstetric and hemostatic measures to minimize maternal and neonatal bleeding risks. The plan should be made available to the mother and all her caregivers in advance of delivery and during delivery and should take into account all eventualities, including preterm delivery. A planned delivery for logistic purposes may be considered, if delivery in a tertiary center remote from the mother's residence is deemed necessary.[89,106]

Intrapartum and postpartum care

Management of labor and mode and place of delivery. For women with severe forms of VWD or carrying a baby potentially at risk of severe VWD, or those with complicated pregnancies, delivery should be planned in a tertiary maternity unit affiliated with an HTC to facilitate timely input from healthcare professionals experienced in the management of such women and their neonates, access to hemostatic agents including factor concentrates and laboratory tests. The mode of delivery is, in general, guided by obstetric indications. However, neonates potentially affected by severe VWD (type 2, type 3) can be at risk of cranial bleeding during labor and delivery, thus the mode of delivery should be considered carefully and individually taking into account fetal and maternal risks. Risks and benefits of a planned Cesarean delivery *versus* vaginal delivery should be considered and discussed with the mother. Late prenatal diagnosis by third-trimester amniocentesis (when the genetic mutation is known) can be considered to guide management of labor and delivery in women carrying a fetus potentially at risk of severe VWD.[89,106] When vaginal delivery is planned, use of invasive fetal monitoring such as application of a fetal scalp electrode and fetal blood sampling and instrumental deliveries, specifically ventouse extraction, should be avoided for such fetuses.[89,106] Ventouse extraction is associated with the highest risk of cranial bleeding and its use should, therefore, also be avoided in fetuses with type 1 and non-severe VWD, although in these cases a fetal scalp electrode and fetal blood sampling and low forceps delivery can be used.[89]

Neuraxial analgesia/anesthesia (neuraxial block). The use of neuraxial block, including neuraxial analgesia and anesthesia, in women with VWD for pain management in labor and for anesthesia for Cesarean sections remains controversial with considerable variation among healthcare pro-

fessionals in relation to its suitability and safety. A survey of 139 healthcare professionals from 39 countries showed differing practices internationally and among individual healthcare professionals, with a considerable proportion of the professionals considering neuraxial block unsuitable regardless of type of VWD, factor levels and clotting factor concentrate supplementation.[83] Thus, many women with VWD may unnecessarily be denied this effective form of pain relief and subjected to risks of general anesthesia. The main concern is increased risk of spinal/epidural hematoma.[110] The rate of this complication is very low in the general obstetric population (1/68,000). The data on this risk in women with VWD, especially those with type 2 and 3, are limited, reflecting a lack of evidence to support definitive recommendations and guidelines. Small case series have demonstrated a safe use of these procedures when factor levels are normalized due to physiological changes of pregnancy or with appropriate clotting factor concentrate supplementation.[43] However, some argue that hemostasis cannot be reliably achieved in women with type 2 or 3 VWD with supplementation of clotting factor concentrate, even when a normal laboratory measurement of VWF activity is achieved and, therefore, recommend against neuraxial block for these women.[43,89,111]

The ASH ISTH NHF WFH guidelines on the management of VWD recommend a target VWF activity of 50-150 IU/dL for the placement of a neuraxial block, and that VWF activity should be maintained above 50 IU/dL while the neuraxial catheter is in place and for at least 6 hours after its removal.[43] However, the guidelines do not provide any recommendations on the suitability of neuraxial blockade and the process of decision-making in different types of VWD. Until the emergence of better evidence, the expert consensus is that neuraxial analgesia and anesthesia should be avoided in women with VWF activity <50 IU/dL unless the hemostatic defect has been corrected with appropriate factor replacement.[43,89] For women with type 1 mild/moderate VWD, the VWF level often reaches normal (>50 IU/dL) in the third trimester of pregnancy and TXA administration is sufficient hemostatic cover;[89] those with a more severe form of VWD require an individualized risk assessment and planning by the multidisciplinary team including an anesthesiologist and hematologist to help the mother make an informed decision. Other options for pain relief in labor (complementary and pharmacological) should be considered and discussed with the mother. For a Cesarean delivery the only alternative option is general anesthesia, which is associated with a high risk in pregnant women especially during an emergency Cesarean section and in high-risk mothers such as those with a high body mass index. The risks of difficulty in intubation, aspiration pneumonia and higher risk of venous thromboembolism and PPH with general anesthesia should be weighed against the potential risk of spinal hematomas. Table 3 provides conditions for the use of regional blocks during labor and delivery in women with inherited bleeding disorders.[112]

Prevention and management of postpartum hemorrhage

Prevention and management of PPH require a robust multidisciplinary obstetric and hemostatic plan with measures addressing obstetric causes of PPH in parallel with correction of the hemostatic defect. The plan should be documented in the mother's clinical notes and distributed to all involved in her care at the time of delivery and in the postpartum period.

Obstetric measures

Uterine atony remains the commonest cause of PPH even in women with VWD, thus active management of the third stage of labor (including controlled cord traction to expedite placental delivery and the use of prophylactic uterotonics administered at the time of delivery) is crucial for reducing blood loss at delivery and the risk of PPH. In women with severe bleeding disorders use of additional uterotonics is recommended.[89,106,113] Monitoring of blood loss by semi-quantitative methods, such as graduated containers and gravimetric weight measurement of blood on drapes and swabs (converting 1 g to 1 mL), provide a more accurate estimation of blood loss compared to the traditional subjective visual assessment and assist in early detection of

Table 3. Conditions for the use of a regional block in women with inherited bleeding disorders during labor and delivery.

1. Multidisciplinary management involving hematologists, anesthetists, obstetricians, and the mother.
2. Detailed counseling on the benefits and risks of neuraxial block and its alternatives to help the mother make an informed decision.
3. Careful assessment of coagulation status, including assessment of clotting factor during third trimester, and bleeding phenotype, including personal and family bleeding history.
4. Availability of therapeutic products and laboratory facilities to ensure adequate response to treatment.
5. Plan of management made antenatally during the third trimester, clearly documented, and readily available to professionals attending the woman in labor.
6. Normalization of the coagulation defect by either pregnancy-induced rise in coagulation factors or the use of appropriate prophylactic treatment prior to regional block procedures.
7. Meticulous technical skills in the administration of regional block by an experienced anesthetist.
8. When an epidural catheter is placed, maintenance of adequate hemostasis prior to catheter removal, as the risk of bleeding is no less than with insertion.
9. Awareness and surveillance for symptoms and signs of potential complications.

PPH. This approach is now recommended for all delivering mothers and especially those at risk, such as women with VWD.[19] Other measures to reduce blood loss and lower the risk of PPH include timely and adequate surgical hemostasis of any surgical wounds such as episiotomies, vaginal tears and Cesarean section wounds. Similarly, retained placenta/placental pieces should be recognized and managed without any delay. Once PPH is diagnosed, management should follow the protocol for PPH, including the use of medical, mechanical, radiological and surgical interventions to control the bleeding in close collaboration with HTC staff to manage hemostatic treatments, discussed below.

The plan to prevent and manage secondary PPH should include diagnosis and correction of iron deficiency and anemia before the mother is discharged from the hospital. The mother and community healthcare professionals involved in her care after discharge should be made aware of the risk of secondary PPH, the plan for hemostatic treatments during the puerperium and a pathway for easy access to input from the obstetric team and the HTC staff when required. A postnatal follow-up 6-8 weeks after delivery provides an excellent opportunity to address a mother's concerns including those related to bowel and bladder function, breastfeeding, postnatal depression, resumption of sexual intercourse and contraception.

Hemostatic management

The correction of coagulation defects with appropriate hemostatic agents is an essential aspect of management during labor and delivery for the prevention of PPH and safe provision of neuraxial block. Treatment options include TXA, desmopressin, and VWF-containing concentrates. The treatment regime and its duration are determined based on maternal bleeding risk after assessing the woman's third trimester VWF and FVIII levels and bleeding phenotype, her obstetric risk factors for PPH such as uterine fibroids, multiple pregnancy, and placenta previa; the planned mode of delivery and type of analgesia and anesthesia for delivery should also be taken in consideration as a higher level of hemostatic cover is required for a Cesarean delivery and when neuraxial block is planned compared to a normal vaginal delivery.

TXA is the recommended hemostatic agent for delivery and the postpartum period in women with a VWF level of at least 50 IU/dL: a dose of 1 g is given once the mother is in established labor[90] and repeated every 6 hours, then continued for 4-6 weeks postpartum to mitigate the risk of secondary PPH. The intravenous route of administration is preferred during labor because of slower gastric emptying and increased risk of vomiting, especially prior to and for 24 hours after neuraxial analgesia/anesthesia or operative deliveries. TXA is also used in combination with other hemostatic treatments (DDAVP or factor concentrate) for women with third trimester VWF activity <50 IU/ dL.[107]

Desmopressin is a treatment option for women with type 1 VWD and selected type 2 VWD with baseline VWF and FVIII levels higher than 10 IU/dL, but a prior test dose is recommended because of variability in response to this agent. Desmopressin is contraindicated in type 2B VWD because it can exacerbate thrombocytopenia due to an increase in platelet binding and it is not used in type 3 VWD because of lack of response.[111] In a recent systematic review including 273 pregnancies in women with inherited bleeding disorders, 212 of whom were women with VWD, desmopressin was safe and effective in preventing and managing PPH especially in VWD.[38] Side effects were reported in two mothers: one case of hyponatremia and water intoxication seizure and a second pregnancy with transient neurological symptoms.[114] Thus, fluid intake should be limited to 1.5 L for 24 hours following desmopressin administration, repeated dosing should be avoided and monitoring of fluid intake and output and electrolytes may be required for women receiving intravenous fluids and for those in whom oxytocin is used for induction or augmentation of labor.

Prophylactic cover with clotting factor concentrate is required in severe VWD, in those with factor levels <50 IU/dL at term and type 2 and 3 VWD. There is a lack of clear guidance on the recommended peak target VWF and FVIII activity levels and laboratory monitoring for women receiving clotting factor concentrate for the prevention of PPH. In general, a target level of 100-150 IU/dL is recommended at delivery, and a trough level should be maintained above 50 IU/dL until hemostasis is secured (5 days following vaginal delivery and 7-10 days after Cesarean section).[43,88,89,100] Monitoring of pre- and post-treatment levels of VWF and FVIII levels is recommended to ensure hemostatic levels are attained.[89,106] Monitoring platelet counts and platelet transfusion are also recommended to maintain the platelet count >50x10^9/mL in type 2B VWD.

Several studies have documented increased blood loss and higher rates of PPH in women with VWD despite factor replacement, possibly due to inadequate clotting factor concentrate cover or to increased consumption and reduced half-life of VWF and FVIII in parturient mothers.[88,100] Additionally, the rate of PPH remains higher in women with factor levels >50 IU/dL, leading the Dutch national guideline in 2017 to increase the factor level cutoff for peripartum clotting factor concentrate prophylaxis to >80 IU/dL and raise the target level to 150 IU/dL to meet the much higher physiological levels seen in women without VWD.[101] Since then, a Dutch study, "The PRegnancy and Inherited bleeding DisordErS" study (NTR: NL6770)" has started a prospective data collection to assess PPH in VWD, and the impact of increasing clotting factor levels on the incidence of PPH.

The choice of VWF factor concentrate, including plasma-derived or recombinant VWF, with differing ratios of VWF and FVIII (Table 2), will depend on local availability and FVIII levels in the third trimester. High purity concentrates with a low FVIII content or recombinant VWF concentrate are advisable for women with a high third trimester FVIII level,

e.g., some women with type 2 VWD, to avoid accumulation of FVIII and associated risk of venous thromboembolism with repeated dosing. Recombinant VWF concentrate is now licensed for use in several countries, but data are limited in relation to its use in pregnancy and the peripartum period. In a small study of 12 deliveries in women with VWD, there was no difference in frequency of PPH between women receiving recombinant or plasma-derived VWF.[115] To minimize risk of secondary PPH, VWF concentrate may be required for a few weeks after delivery in women with severe VWD, especially type 3 VWD. In addition, TXA 1 g six hourly should be continued during the puerperium (4-6 weeks) until the lochia stops.

Pregnancy and the postpartum period are associated with an increased risk of venous thromboembolism. Women with VWD were no less likely to experience a pulmonary embolism after childbirth than women without VWD.[93] Therefore, women, especially those receiving factor concentrate, should be carefully assessed and appropriate postnatal prophylaxis against venous thromboembolism should be advised. Mechanical methods should be employed, and low-molecular-weight heparin should be considered in high-risk women, with adequate correction of VWF and FVIII levels.[89,106]

Management of the neonate

The diagnosis of mild/moderate VWD is difficult in neonates because of physiologically increased VWF levels at birth and in the first few months of life.[116] However, normal values of VWF can exclude severe type 1 and types 2 and 3 VWD in the neonate. For neonates at risk of severe VWD, a cord blood sample should be obtained and sent to the hemophilia laboratory for assessment of VWF and FVIII levels and the parents should be informed of the test result and subsequent management for their newborn. Neonates diagnosed with severe VWD can be at risk of bleeding from intramuscular injection and should receive vitamin K orally and immunization via a subdermal route. Registration and follow-up with the HTC should be arranged. For neonates at risk of mild/moderate VWD, the diagnosis can be deferred unless there is a clinical indication (e.g., if the neonate requires surgery) and vitamin K and immunizations can be given via the intramuscular route.[89]

The future outlook for women with von Willebrand disease and other inherited bleeding disorders

Clinical research and trials

Important principles to consider in planning for future research in women with VWD are to include women in clinical trials[27] and to address VWD-specific issues in trials.[21] These trials should incorporate principles of care for women[25] and assure that women's issues are addressed and recognized in research.[21] With their lived experience, women with VWD offer tremendous potential not only through their participation in clinical trials but also by their contribution to trial design and advocacy, promoting women's issues in research.[21,26,27] The goal of VWD-specific research should be to assure that trial endpoints are feasible and patient-focused. As VWD is a rare disease, clinical trials should include novel designs, a core set of clinical outcomes and feasible, patient-focused trial endpoints.[117] Trials should be optimized by rare disease design, and diversity, equity, and inclusion should be integrated into every trial.[118] Efforts should be made to harmonize demographic terminology, and enhance awareness of implicit bias in enrollment, eligibility criteria, and adoption of novel approaches to enhance success, e.g., running trials within medical records, at the HTC, involving community physicians and support staff, so that patient care and research can be linked for advocacy, policy, and funding.[26]

Transformative insights for hematology

So, what are the implications and insights of treatment and research in women with bleeding disorders and solutions to the problem of HMB which could transform hematology? The critical themes that are recognized for the care of women with HMB in hematology, if not all medicine, are to include women in all research including new drug development while maintaining careful surveillance for safety (fertility, teratogenicity, thrombosis) when adapting therapeutics for the treatment of women.[23] The patients' perspective is central to opening up dialogue with women concerning their treatment preferences and reproductive plans. Their care should be comprehensive and involve a family history and genetic testing and, given the pervasive burden of iron deficiency in these women, standardization of screening, testing, and treatment is essential. To accomplish these goals and move into the next 100 years of VWD management will require prospective clinical trials and data collection to better understand the problems in order to design better markers, outcome measures, therapeutics, and guidelines. These goals and the model of a multidisciplinary support team should help to overcome obstacles, find care, identify approaches to promote health and improve outcomes for women with other hematologic and medical diseases.

Conclusion and future directions

In this the 100th year since the first description of VWD, there have been significant advances and improvements in the care of women with VWD. Nevertheless, care for women lags, with delay in diagnosis, inadequate access to care, insufficient therapies to reduce HMB, and exclusion from research studies. While the last 5 years have witnessed

international efforts and collaborations to improve the management of women with VWD, including international guidelines and principles of care for affected women,[25,43] continued research is needed to address knowledge gaps and provide data to support evidence-based management guidelines. Inclusion of women in clinical trials is essential in order to assess the efficacy and safety of new treatment options in the management of obstetric and gynecologic bleeding and widen the therapeutic choices of women. Efforts must also continue to increase awareness and education of women and healthcare professionals as well HTC staff about challenges faced by women and the provision of optimal care to improve the health and quality of care and life of women.

Disclosures

RA-K has received education grants, honoraria, and lecture fees from Takeda Pharmaceuticals, Pharmacosmos, and CSL Behring. MVR acknowledges research support to the University of Pittsburgh from BioMarin, Sanofi, Spark Therapeutics, and Takeda Pharmaceuticals, and has served as a consultant for Alnylam, BeBio, BioMarin, HEMAB, the Institute for Economic Review (ICER), and the Foundation for Women and Girls with Bleeding Disorders.

Contributions

RA-K and MVR jointly developed the concept of this review article, performed the literature search, and wrote the manuscript.

References

1. von Willebrand E. Hereditär pseudohemophili. Finiska Läkarsällskapets Handl. 1926;67:7-112.
2. Ragni MV, Bontempo FA, Hassett AC. von Willebrand disease and bleeding in women. Haemophilia. 1999;5(5):313-317.
3. Kadir RA, Economides DL, Sabin CA, Pollard D, Lee CA. Assessment of menstrual blood loss and gynecological problems in patients with inherited bleeding disorders. Haemophilia. 1999;5(1):40-48.
4. Hallberg L, Milsson L. Determination of menstrual blood loss. Scand J Lab Invest. 1964;16:244-248.
5. Curry N, Bowles L, Clark TJ, et al. Gynecological management of women with inherited bleeding disorders. A UK Haemophilia Centres Doctors' Organisation Guideline. Haemophilia. 2022;28(6):917-937.
6. Laffan M, Sathar J, Johnsen JM. Von Willebrand disease: diagnosis and treatment of women, and genomic approach to diagnosis. Haemophilia. 2021;27(Suppl 3):66-74.
7. Tosetto A, Castaman G, Rodeghiero F. Evidence-based diagnosis of type 1 von Willebrand disease: a Bayes theorem approach. Blood. 2008;111(8):3998-4003.
8. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited disorders. J Thromb Haemost. 2010;8(9):2063-2065.
9. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynecol. 1990;97(8):734-739.
10. Halimeh S, Rott H, Kappert G. PBAC score: an easy-to-use tool to predict coagulation disorders in women with idiopathic heavy menstrual bleeding. Haemophilia. 2016;22(3):e217-e220.
11. Biss TT, Blanchette VS, Clark DS, et al. Quantitation of bleeding symptoms in children with von Willebrand disease: use of a standardized pediatric bleeding questionnaire. J Thromb Haemost. 2010;8(5):950-956.
12. Reid PC, Coker A, Coltart R. Assessment of menstrual blood loss using a pictorial chart. A validation study. BJOG. 2000;107(3):320-322.
13. Warner PE, Critchley HO, Lumsden MA, Campbell-Brown M, Douglas A, Murray GD. Menorrhagia I: measured blood loss, clinical features, and outcome in women with heavy periods: a survey with follow-up data. Am J Obstet Gynecol. 2004;190(5):1216-1223.
14. Philipp CS, Faiz A, Heit JA, et al. Evaluation of a screening tool for bleeding disorders in a US multisite cohort of women with menorrhagia. Am J Obstet Gynecol. 2011;204(3):209.e1-7.
15. Doherty D, Grabell J, Christopherson PA, et al. Variability in the Thrombosis and Haemostasis-Scientific and Standardization Committee endorsed Bleeding Assessment Tool (ISTH-BAT) score with normal aging in healthy females: contributory factors and clinical significance. J Thromb Haemost. 2023;21(4):880-886.
16. Lavin M, Aguila S, Dalton N, et al. Significant gynecological bleeding in women with low von Willebrand factor levels. Blood Adv. 2018;2(14):1784-1791.
17. Rodeghiero F, Pabinger I, Ragni M, et al. Fundamentals for a systematic approach to mild and moderate inherited bleeding disorders: an EHA Consensus Report. Hemasphere. 2019;3(4):e286.
18. The National Institute for Health and Care Excellence. Heavy menstrual bleeding: assessment and management. Guidance. https://www.nice.org.uk/guidance/ng88 Accessed on March 10, 2025.
19. Connell NT, James PD, Brignardello-Petersen R, et al. von Willebrand disease: proposing definitions for future research. Blood Adv. 2021;5(2):565-569.
20. Noone D, Skouw-Rasmussen N, Lanvin M, van Galen KV, Kadir R. Barriers and challenges faced by women with congenital bleeding disorders in Europe: results of a patient survey conducted by the European Haemophilia Consortium. Haemophilia. 2019;25(3):468-474.
21. O'Donnell MJ, Kadir RA, van Galen KPM, Lavin M, EAHAD Women and Girls Working Group. Are women welcome in haemophilia trials? Haemophilia. 2025;31(3):575-577.
22. Atiq F, Boender J, van Heerde WL, et al. Importance of genotyping in von Willebrand disease to elucidate pathogenic mechanisms and variability in phenotype. Hemasphere. 2022;6(6):e718.
23. Sadler B, Minard CG, Haller G, et al. Whole-exome analysis of adolescents with low VWF and heavy menstrual bleeding identifies novel genetic associations. Blood Adv. 2022;6(2):420-428.
24. Munro MG, Mast AE, Powers JM, et al. The relationship between heavy menstrual bleeding, iron deficiency, and iron deficiency anemia. Am J Obstet Gynecol. 2023;229(1):1-9.

25. van Galen K, Lavin M, Skouw-Rasmussen N, et al. European Haemophilia Consortium (EHC) and the European Association for Haemophilia and Allied Disorders (EAHAD). European principles of care for women and girls with inherited bleeding disorders. Haemophilia. 2021;27(5):837-847.
26. Baldwin MK, Ahmadzia HK, Bartlett DL, et al. Building the foundation for a community-generated national research blueprint for inherited bleeding disorders: research to advance the health of people with inherited bleeding disorders with the potential to menstruate. Expert Rev Hematol. 2023;16(sup1):71-86.
27. Fedewa SA, Cafuir L, Valentino LA, Koo A, Antun A, Kempton CL. Women and girls' participation in haemophilia clinical trials. Haemophilia. 2024;30(6):1440-1443.
28. Clearfield E, Kim B, Ford S, et al. A core outcome set for prophylaxis and perioperative treatment of von Willebrand disease: the core VWD initiative. Haemophilia. 2024;30(6):1357-1365.
29. Kadir RA, Tarawah A, Shridhar N, Kulkarni R. Driving improvement of diagnosis and awareness of heavy menstrual bleeding in women among physicians. Haemophilia. 2024;30(5):1185-1192.
30. Huguelet PS, Ayala KA, Beaty L, et al. Knowledge and confidence of obstetrics and gynecology residents in the evaluation and management of heavy menstrual bleeding due to inherited bleeding disorders. Womens Health Rep (New Rochelle). 2024;5(1):705-711.
31. Vo KT, Grooms L, Klima J, Holland-Hall C, O'Brien SH. Menstrual bleeding patterns and prevalence of bleeding disorders in a multidisciplinary adolescent hematology clinic. Haemophilia. 2013;19(1):71-75.
32. Peuranpää P, Heliövaara-Peippo S, Fraser I, Paavönen J, Hurskainen R. Effects of anemia and iron deficiency on quality of life in women with heavy menstrual bleeding. Acta Obstet Gynecol Scand. 2014;93(7):654-660.
33. Castaman G, Katsarou O, Jansen N, Santos S, Escolar G, Berntorp E. Clinical, economic, and health-related quality of life burden associated with von Willebrand disease in adults and children: systematic and targeted literature reviews. Haemophilia. 2023;29(2):411-422.
34. Bruner AB, Joffee A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anemic iron-deficient adolescent girls. Lancet. 1996;348(9033):992-996.
35. De Loughery TG. Safety of oral and intravenous iron. Acta Haematol. 2019;142(1):8-12.
36. McCormick M, Hu J, Chandler M, Manuel M, Chrisentery-Singleton T, Ragni MV. Iron ladies: prevalence and risk factors for iron deficiency in women with bleeding disorders. Haemophilia. 2025 2025;31(3):502-508.
37. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women. Lancet Haematol. 2017;4(11):e524-e533.
38. Cogan JC, Meyer J, Jian Z, Sholzberg M. Iron deficiency resolution and time to resolution in an American health care system. Blood Adv. 2024;8(23):6029-6034.
39. James A, Ragni MV, Picozzi VJ. ASH Special educational symposium: bleeding disorders in premenopausal women: another public health crisis for hematology. Hematology Am Soc Hematol Educ Program. 2006:474-485.
40. Weyand AC, Chaitoff A, Freed GL, Sholzberg M, Choi SW, McGann PT. Prevalence of iron deficiency and iron deficiency anemia in US females aged 12-21 years. 2003-2020. JAMA. 2023;329(24):2191-2193.
41. Mansour D, Hofmann A, Gemzell-Danielsson K. A review of clinical guidelines on the management of iron deficiency and iron deficiency anemia in women with heavy menstrual bleeding. Adv Ther. 2021;38(1):201-225.
42. [No authors listed]. Screening and management of bleeding disorders in adolescents with heavy menstrual bleeding. ACOG Committee opinion, number 875. Obstet Gynecol. 2019;134(3):e71-e83.
43. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv. 2021;5(1):301-325.
44. The American Society of Hematology. Plan for new ASH clinical practice guidelines on iron deficiency anemia. https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/iron-deficiency-anemia Accessed on Feb 12, 2024.
45. Kadir RA, Sabin CA, Pollard D, Lee CA, Economides DL. Quality of life during menstruation in patients with inherited bleeding disorders. Haemophilia. 1998;4(6):836-841.
46. Srivaths L, Minard CG, O'Brien SH, et al. The spectrum and severity of bleeding in adolescents with low von Willebrand factor-associated heavy menstrual bleeding. Blood Adv. 2020;4(13):3209-3216.
47. von Mackensen S. Quality of life in women with bleeding disorders. Haemophilia. 2011;17(Suppl 1):33-37.
48. Xu Y, Deforest M, Grabell J, Hopman W, James P. Relative contributions of bleeding scores and iron status on health-related quality of life in von Willebrand disease: a cross-sectional study. Haemophilia. 2017;23(1):115-121.
49. Govorov I, Ekelund L, Chaireti R, et al. Heavy menstrual bleeding and health-associated quality of life in women with von Willebrand disease. Exp Therapeutic Med. 2016;11(5):1923-1929.
50. Wyatt SN, Banahan T, Tang Y, Nadendla K, Szychowski JM, Jenkins TR. Effect of radiofrequency endometrial ablation on dysmenorrhea. J Minim Invasive Gynecol. 2016;23(7):1163-1166.
51. Kadir RA, Edlund M, von Mackensen S. The impact of menstrual disorders on quality of life in women with inherited bleeding disorders. Haemophilia. 2010;16(5):832-839.
52. Samuelson-Bannow B, Haley K, Colwill A, Edelman A, Bednarek P, Baldwin M. Adult haematology clinics for menstruating/pregnant patients: a single center experience and lessons learned. Haemophilia. 2024;30(2):564-566.
53. Turan P, Gomez K, Kadir RA. Review of interventions and effectiveness for heavy menstrual bleeding in women with moderate and severe von Willebrand disease. Haemophilia. 2024;31(5):1177-1184.
54. Amesse LS, Pfaff-Amesse T, Leonardi R, Uddin D, French JA II. Oral contraceptives and DDAVP nasal spray: patterns of use in managing VWD-associated menorrhagia: a single-institution study. J Pediatr Hematol Oncol. 2005;27(7):357-363.
55. Foster PA. The reproductive health of women with von Willebrand disease unresponsive to DDAVP: results of an international survey (ISTH). Thromb Haemost. 1995;74(2):784-790.
56. Brignardello-Petersen R, Alayli AE, Husainat N, et al. Gynecologic and obstetric management of women with von Willebrand disease: summary of 3 systematic reviews of the literature. Blood Adv. 2022;6(1):228-237.

57. Kingman CE, Kadir RA, Lee CA, Economides DL. The use of levonorgestrel-releasing intrauterine system for treatment of menorrhagia in women with inherited bleeding disorders. BJOG. 2004;111(12):1425-1428.
58. Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL. DDAVP nasal spray for treatment of menorrhagia in women with inherited bleeding disorders: a randomized placebo-controlled crossover study. Haemophilia. 2002;8(6):787-793.
59. Rose SS, Faiz A, Miller CH, Saidi P, Philipp CS. Laboratory response to intranasal desmopressin in women with menorrhagia and platelet dysfunction. Haemophilia. 2008;14(3):571-578.
60. Kouides PA, Byams VR, Philipp CS, et al. Multisite management study of menorrhagia with abnormal laboratory haemostasis: a prospective crossover study of intranasal desmopressin and oral tranexamic acid. Br J Haematol. 2009;145(2):212-220.
61. Ettinghausen CE, Lassila R, Escolar G, et al. Plasma-derived von Willebrand factor/factor VIII concentrate (Haemate P) in von Willebrand disease: a systematic review and pharmacovigilance update. Haemophilia. 2025;31(2):247-262.
62. Ragni MV, Machin N, Malec LM, et al. Von Willebrand factor for menorrhagia: a survey and literature review. Haemophilia. 2016;22(3):397-402.
63. Ragni MV, Rothenberger S, Feldman R, et al. Multicenter, randomized, crossover trial comparing recombinant von Willebrand factor and tranexamic acid for heavy menstrual bleeding in von Willebrand disease. Lancet Haematol. 2023;10(8):e612-e623.
64. Beelen P, Reinders IMA, Scheepers WFW, et al. Prognostic factors for the failure of endometrial ablation: a systematic review and meta-analysis. Obstet Gynecol. 2019;134(6):1269-1281.
65. Brignardello-Petersen R, Alayli EA, Husainat N, et al. Surgical management of patients with von Willebrand disease: summary of 2 systematic reviews of the literature. Blood Adv. 2022;6(1):121-128.
66. Eising HP, Punt MC, Leemans JC, Bongers MY. Prophylactic and therapeutic strategies for intraoperative bleeding in women with von Willebrand disease and heavy menstrual bleeding: a systematic review. Blood Rev. 2023;62:101131.
67. von Drygalski A, Chowdary P, Kulkarni R, et al. XTEND-1 Trial Group. Efanesoctocog alfa prophylaxis for patients with severe hemophilia A. N Engl J Med. 2023;388(4):310-318.
68. Ryu JH, Bauer KA, Schulman S. Periprocedural management of type 2N von Willebrand disease with efanesoctocog alfa. J Thromb Haemost. 2023;21(12):3058-3510.
69. Callahan MU, Negrier C, Pza-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. Blood. 2021;137(16):2231-2242.
70. Yaoi H, Shida Y, Katazawa T, Shima M, Nogami K. Emicizumab improves thrombus formation of type 2A von Willebrand disease under high thrombus formation of type 2A von Willebrand disease under high shear condition. Haemophilia. 2021;27(2):e194-e203.
71. Weyand AC, Flood VH, Shavit JA, Pipe SWS. Efficacy of emicizumab in a pediatric patient with type 3 von Willebrand disease and alloantibodies. Blood Adv. 2019;3(18):2748-2750.
72. Chion A, Byrbe C, Atiq F, et al. The aptamer BT200 blocks interaction of K1405-K1408 in the VWF-A1 domain with macrophage LRP1. Blood. 2024;144(13):1445-1456.
73. Ay C, Pabinger I, Kovacevic KD, et al. The VWF binding aptamer rondoraptivon pegol increases platelet counts and VWF/FVIII in type 2B von Willebrand disease. Blood Adv. 2022;6(18):5467-5476.
74. McCluskey G, Heestermans M, Peyron I, et al. A fully humanized von Willebrand disease type 1 mouse model as unique platform to investigate novel therapeutic options. Haematologica. 2024;110(4):923-937.
75. Leong L, Byun T, Kim B, et al. Preclinical characterization of VGA039, an anti-protein S monoclonal antibody being developed as a universal hemostatic agent for various bleeding disorders. Blood. 2022;140(Suppl 1):1666-1667.
76. Gandhi PS, Zivkovic M, Østergarard H, et al. HMB-001, a novel bispecific antibody approach for the potential prophylactic treatment of inherited bleeding disorders. Nat Cardiovasc Res. 2024;3(2):166-185.
77. Roullet S, Luc N, Rayes J, et al. Efficacy of platelet-inspired hemostatic nanoparticles on bleeding in von Willebrand disease models. Blood. 2023;141(23):2891-2900.
78. de Jong A, Dirven RJ, Boender J, et al. Ex vivo improvement of a von Willebrand disease type 2A phenotype using an allele-specific small interfering RNA. Thromb Haemost. 2020;120(11):1569-1579.
79. Campioni M, Legendre P, Loubiere C, et al. In vivo modulation of a dominant-negative variant in mouse models of von Willebrand disease type 2A. J Thromb Haemost. 2021;19(1):139-146.
80. Linthorst NA, Jongejan YK, Dirven RJ, et al. Amelioration of a von Willebrand disease type 2B phenotype in vivo upon treatment with allele-selective siRNAs. Blood Adv. 2024;9(2):310-320.
81. Jongejan YK, Echeverri ES, Dirven RJ, et al. Small interfering RNA-mediated allele-selective silencing of von Willebrand factor in vitro and in vivo. Blood Adv. 2023;7(20):6108-6119.
82. Barbon E, Kawecki C, Marmier S, et al. Development of a dual hybrid AAV vector for endothelial-targeted expression of von Willebrand factor. Gene Ther. 2023;30(3-4):245-254.
83. Lavin M, Sánchez Luceros A, Kouides P, et al. Examining international practices in the management of pregnant women with von Willebrand disease. J Thromb Haemost. 2022;20(1):82-91.
84. Kadir R, Lee C, Sabin C, Pollard D, Economides D. Pregnancy in women with von Willebrand's disease or factor XI deficiency. Br J Obstet Gynaecol. 1998;105(3):314-321.
85. Delbrück C, Miesbach W. The course of von Willebrand factor and factor VIII activity in patients with von Willebrand disease during pregnancy. Acta Haematol. 2019;142(2):71-78.
86. Castaman G. Changes in von Willebrand factor during pregnancy in women with and without von Willebrand's disease. Mediterr J Hematol Infect Dis. 2013;5(1):e2013052.
87. Huq F, Kulkarni A, Agbim E, Riddel A, Tuddenham E, Kadir R. Changes in the levels of factor VIII and von Willebrand factor in the puerperium. Haemophilia. 2011;18(2):241-245.
88. James A, Konkle B, Kouides P, Ragni M, Thames B, Gupta S. Postpartum von Willebrand factor levels in women with and without von Willebrand disease and implications for prophylaxis. Haemophilia. 2015;21(1):81-87.
89. [No authors listed]. Management of inherited bleeding disorders in pregnancy: green-top guideline No. 71. BJOG. 2017;124(8):e193-e263.
90. Shahbazi S, Moghaddam-Banaem L, Ekhtesari F, Ala F. Impact of inherited bleeding disorders on pregnancy and postpartum hemorrhage. Blood Coag Fibrinolysis. 2012;23(7):603-607.
91. Lak M, Peyvandi F, Mannucci P. Clinical manifestations and

complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease. Br J Haematol. 2000;111(4):1236-1239.
92. Skeith L, James P, Kouides P, et al. VWD Pregnancy Loss Study Group. Pregnancy loss in individuals with von Willebrand disease and unspecified mucocutaneous bleeding disorders: a multicenter cohort study. J Thromb Haemost. 2025;23(2):429-439.
93. James A, Jamison M. Bleeding events and other complications during pregnancy and childbirth in women with von Willebrand disease. J Thromb Haemost. 2007;5(6):1165-1169.
94. Calleja-Agius J, Custo R, Brincat M, Calleja N. Placental abruption and placenta praevia. Eur Clinics Obstet Gynaecol. 2006;2:121-127.
95. Ito M, Yoshimura K, Toyoda N, Wada H. Pregnancy and delivery in patients with von Willebrand's disease. J Obstet Gynaecol Res. 1997;23(1):37-43.
96. Briley A, Seed PT, Tydeman G, et al. Reporting errors, incidence and risk factors for postpartum haemorrhage and progression to severe PPH: a prospective observational study. BJOG. 2014;121(7):876-888.
97. Tort J, Rozenberg P, Traoré M, Fournier P, Dumont A. Factors associated with postpartum hemorrhage maternal death in referral hospitals in Senegal and Mali: a cross-sectional epidemiological survey. BMC Pregnancy Childbirth. 2015;15:235.
98. Punt M, Waning ML, Mauser-Bunschoten EP, et al. Maternal and neonatal bleeding complications in relation to peripartum management in women with von Willebrand disease: a systematic review. Blood Rev. 2020;39:100633.
99. Castaman G, James P. Pregnancy and delivery in women with von Willebrand disease. Eur J Haematol. 2019;103(2):73-79.
100. Stoof S, van Steenbergen H, Zwagemaker A, et al. Primary postpartum haemorrhage in women with von Willebrand disease or carriership of haemophilia despite specialised care: a retrospective survey. Haemophilia. 2015;21(4):505-512.
101. Punt M, van Leusden F, Bloemenkamp K, et al. Primary postpartum hemorrhage in women with von Willebrand disease and carriers of hemophilia: a retrospective analysis. Res Pract Thromb Haemost. 2024;8(5):102508.
102. Govorov I, Löfgren S, Chaireti R, Holmström M, Bremme K, Mints M. Correction: postpartum hemorrhage in women with von Willebrand disease - a retrospective observational study. PLoS One. 2016;12(2):e0172185.
103. Kulkarni A, Osmond M, Bapir M, Riddell A, Smith C. The effect of labour on the coagulation system in the term neonate. Haemophilia. 2013;19(4):533-538.
104. Dupervil B, Abe K, O'Brien SH, et al. Characteristics, complications, and sites of bleeding among infants and toddlers less than 2 years of age with VWD. Blood Adv. 2021;5(8):2079-2086.
105. Sanders Y, Fijnvandraat K, Boender J, et al. Bleeding spectrum in children with moderate or severe von Willebrand disease: relevance of pediatric-specific bleeding. Am J Hematol. 2015;90(12):1142-1148.
106. Huq F, Kadir R. Management of pregnancy, labour and delivery in women with inherited bleeding disorders. Haemophilia. 2011;17 Suppl 1:20-30.
107. Jawad A. Tranexamic acid for antenatal bleeding of unknown origin in the second and third trimesters: a prospective clinical trial. Zanco J Medl Sci. 2021;25(2):532-543.
108. Sharma R., Chatterjee S., Kapur A, Pandit S. To study the effect of tranexamic acid in early pregnancy bleeding in post IVF pregnancies: a prospective observational study. Int J Curr Adv Res. 2019;8(11):20494-20497.
109. Mirza F, Abdul-Kadir R, Breymann C, Fraser I, Taher A. Impact and management of iron deficiency and iron deficiency anemia in women's health. Exp Rev Hematol. 2018;11(9):727-736.
110. Ruppen W, Derry S, McQuay H, Moore RA. Incidence of epidural hematoma, infection, and neurologic injury in obstetric patients with epidural analgesia/anesthesia. Anesthesiology. 2006;105(2):394-399.
111. Laffan M, Lester W, O'Donnell J, Will A, Tait R, Goodeve A. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. Br J Haematol. 2014;167(4):453-465.
112. Bouthors AS, England A, Kadir RA. Analgesia and anaesthesia for pregnant women with inherited bleeding disorders. In: Inherited Bleeding Disorders in Women, Second Edition. Editors Kadir RA, James PD, Lee C. London: John Wiley and Sons Ltd; 2019. p. 191-202.
113. Janbain M, Kouides P. Managing pregnant women with haemophilia and VWD; how we provide optimum care and prevent complications. Intl J Womens Health. 2022;14:1307-1313.
114. Al Arashi W, Romano L, Leebeek F, et al. Desmopressin to prevent and treat bleeding in pregnant women with an inherited bleeding disorder: a systematic literature review. J Thromb Haemost. 2024;22(1):126-139.
115. Machin N, Ragni M. Recombinant vs plasma-derived von Willebrand factor to prevent postpartum hemorrhage in von Willebrand disease. Blood Adv. 2020;4(14):3234-3238.
116. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen D. Development of the human coagulation system in the full-term infant. Blood. 1987;70(1):165-172.
117. van Kwawegen CB, Fijnvandraat K, Kruip MJH, et al. Patient-reported data on the severity of von Willebrand disease. Haemophilia. 2024;30(6):1348-1356.
118. Kuaban A, Croker AK, Keefer J, et al. The roadmap to integrate diversity, equity, and inclusion in hematology clinical trials: an American Society of Hematology initiative. Blood Adv. 2024;9(4):687-694.