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ISTH GUIDANCE & GUIDELINES

Management of women with type 2B von Willebrand disease during pregnancy and postpartum: guidance from ISTH SSC subcommittees on von Willebrand factor and women's health issues in thrombosis and hemostasis

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Abstract

Type 2B von Willebrand disease (VWD) is a rare qualitative variant, accounting for ~5% of all VWD cases. It is characterized by increased affinity of abnormal von Willebrand factor (VWF) for the platelet glycoprotein Ibα receptor, resulting in enhanced clearance of both high-molecular-weight VWF multimers and platelets from circulation. The management of women with type 2B VWD during pregnancy and the postpartum period poses unique challenges due to complex hemostatic abnormalities, a high risk of bleeding complications, and a lack of evidence-based guidelines. A recent

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systematic review, international registry analysis, and global physician survey highlighted several unmet clinical needs in this population, including gaps in early diagnosis, prenatal counseling, pregnancy monitoring, and peripartum management. In response, the International Society on Thrombosis and Haemostasis Scientific Subcommittees on VWF and on Women's Health Issues in Thrombosis and Haemostasis collaborated to develop consensus-based guidance for the management of type 2B VWD in pregnancy and postpartum. Using the real-time Delphi methodology, 14 international experts reviewed 26 initial statements on diagnosis, monitoring, and treatment. After 2 rounds of anonymous voting and revisions based on participants' feedback, consensus was achieved on 25 statements. These consensus statements, grounded in the best available evidence and expert opinion, aim to standardize care, guide management, and improve clinical outcomes for women with type 2B VWD during pregnancy and postpartum.

KEYWORDS
consensus, guidelines, peripartum period, pregnancy complications, von Willebrand diseases

1 | INTRODUCTION

Von Willebrand disease (VWD) is the most common inherited bleeding disorder, caused by either a quantitative (types 1 and 3) or qualitative (type 2) deficiency of von Willebrand factor (VWF). Although clinical presentations are variable, mucocutaneous bleeding is a hallmark across all VWD types [1]. Type 2B VWD is a qualitative type characterized by increased affinity of abnormal VWF for the platelet glycoprotein Ibα (GPIbα) receptor due to gain-of-function changes in the A1 domain of *VWF* [2]. Enhanced interaction between VWF and platelets promotes clearance of high-molecular-weight (HMW) VWF multimers and platelets from circulation, resulting in VWF deficiency and variable degrees of thrombocytopenia [3–8]. Increased susceptibility of 2B VWF to proteolysis by ADAMTS-13 also contributes to the loss of VWF HMW multimers from the circulation [9]. Type 2B accounts for ~5% of all VWD cases and is typically inherited in an autosomal dominant pattern with high penetrance [3]. The laboratory and clinical phenotypes of type 2B VWD vary significantly depending on the specific allelic variant in exon 28 of the A1 domain of the *VWF* gene [10].

A defining laboratory feature is platelet agglutination at lower ristocetin concentrations than in healthy controls and patients with other VWD types [11,12]. Thrombocytopenia is present in 30% to 38% of patients at baseline, but it may develop or worsen under stress (eg, pregnancy, surgery, or inflammation) due to increased production of abnormal VWF. Federici et al. [10] found that platelet count below 140×10^9/L is associated with an ~5-fold increase in bleeding risk, indicating that thrombocytopenia is an independent risk factor for bleeding in patients with 2B VWD. Despite similar functional VWF activity, bleeding in type 2B VWD is generally more severe than in type 2M or type 1 VWD [13]. Pregnancy poses unique challenges in women with type 2B VWD due to the qualitative VWF deficiency and progressive thrombocytopenia, which may become pronounced in late gestation [14,15]. Some type 2B variants also impair platelet function, adding to the bleeding risk [16,17]. The use of desmopressin (DDAVP) is contraindicated because it can exacerbate thrombocytopenia [18]. Bleeding complications—especially postpartum hemorrhage (PPH) are common [19]. In a recent pooled analysis of literature and data from the International Society on Thrombosis and Haemostasis (ISTH)-funded international registry, clinically significant bleeding occurred in 53% of pregnancies even though, in 69% of these pregnancies, prophylactic VWF-containing therapy was applied [20]. Due to the rarity of type 2B VWD and a lack of high-quality data, clinical management during pregnancy and postpartum remains empirical and highly variable [21,22]. Several studies have called for an international consensus to standardize the management and optimize outcomes in this population [20,22,23]. In light of the scarcity of clinical trial evidence, we used the Delphi method to build expert consensus on the diagnosis, monitoring, and treatment of women with type 2B VWD during pregnancy and postpartum.

2 | METHODS

2.1 | Project conception

This was a collaborative joint project between the ISTH Subcommittee on VWF and the ISTH Subcommittee on Women's Health Issues in Thrombosis and Haemostasis. It was initiated by a core expert group and supported by a broad network of international specialists experienced in managing bleeding disorders during pregnancy and the postpartum period. Recent studies have highlighted substantial gaps in evidence and significant variability in the clinical management

of women with type 2B VWD during pregnancy and postpartum [20,22]. Drawing on these findings and their own clinical expertise, the 3 core experts (M.O., R.A.-K., and A.S.-L.) identified key dilemmas and unmet needs in the care of this patient population. As a next step, the core group developed an initial list of 26 guidance statements to serve as the foundation for building expert consensus. By formulating the initial statements, the core group adhered to the predefined criteria, meaning that every statement should be (a) related to some of identified challenges, (b) simply and briefly formulated, (c) based on current guidelines, data from the literature, and expert opinions, and (d) proactive. These preliminary statements underwent a rigorous process of iterative review and refinement. A draft version reflecting full consensus among the 3 core experts was presented and approved at the 2023 ISTH-SSC meeting on VWF in Montreal, Canada. The rationale for each guidance statement included in the Delphi survey is explained in detail in a separate section of this article.

To reach formal consensus, the real-time Delphi (RTD) method was used. This approach, developed by Gordon and Pease [24] not only retains the core features of the classical Delphi method but also enhances efficiency by allowing immediate feedback and eliminating the need for multiple survey rounds. Participants remained anonymous to each other throughout the process but had access to real-time summaries of how each statement was rated, as well as accompanying comments. They could revisit the survey at any time and revise their responses throughout the duration of the Delphi process.

2.2 | Expert panel selection

A total of 25 international experts were invited to participate, selected from the global scientific community based on their extensive experience in the diagnosis and management of inherited bleeding disorders. Representation from developing countries was actively sought while ensuing expertise with type 2B VWD in pregnancy. Eligibility criteria included significant clinical expertise in managing women with type 2B VWD and/or authorship of at least one peer-reviewed publication related to the diagnosis or treatment of type 2B VWD.

Participants were invited to the RTD process using the Foresight Cockpit online software [25]. Upon agreeing to participate, each expert received a secure, individualized access link to the survey platform. This platform provided the finalized guidance statements, relevant background materials, and clear instructions for rating each statement.

2.3 | RTD process

Experts were asked to rate each statement on a 9-point Likert scale from 1 to 3 (inappropriate), 4 to 6 (uncertain), or 7 to 9 (appropriate) based on their evaluation. If they rated a statement as inappropriate or uncertain, they were encouraged to provide brief comments explaining their reasoning. During the initial 4-week period, participants could revisit the survey to view a summary of ratings from other experts who had already completed the survey. This allowed them to potentially adjust their own ratings and add or revise comments. To ensure engagement, two reminder emails were sent during this period, informing participants of the deadline to visit the RTD web page.

2.4 | Data analysis

Four weeks after the statements were disseminated to participants, the core group members conducted a preliminary analysis of the responses. Following the RTD methodology and the criteria outlined by Quirke et al. [26], consensus was considered reached if $\geq$70% of participants rated a statement as appropriate and <15% rated it as inappropriate. If >50% of participants rated a statement below 7, consensus was deemed not to have been reached. If neither of these criteria was met, the consensus was considered undetermined for that statement.

Statements that met the full consensus criteria after the first RTD round were deemed appropriate and excluded from further rating. Statements with undetermined consensus but which included suggestions for revisions were carefully reviewed and revised by the core group. Once consensus was reached among the core group members on the revisions, the updated statements were disseminated to participants in the second RTD round, inviting them to rate the revised statements.

During the next 4 weeks, participants were able to rate the revised statements and could view real-time ratings and comments from other experts, allowing them to adjust their assessments accordingly. It was predetermined that, after the second RTD round, no further revisions would be made to statements that did not achieve consensus. Figure 1 shows the real-time Delphy methodology and the project steps.

3 | RESULTS OF DELPHI STATEMENTS RATING

Of 25 invited experts, 14 (56%) completed both the first and second rounds of the RTD survey. This rate aligns with the 40% to 70% response rate commonly reported in RTD studies [26]. Their responses were analyzed and included in the results. Eleven experts either did not start the rating process or provided incomplete responses, which were excluded from the analysis. Among those who did not participate, 2 abstained from assessing the statements due to lack of confidence in their responses, 4 found the RTD process too complicated or demanding, and 5 did not provide any reasons for their nonparticipation. The experts who completed the survey were from the following countries: 3 from Canada, 3 from the Netherlands, 2 from the United States, and 1 each from Argentina, Australia, the

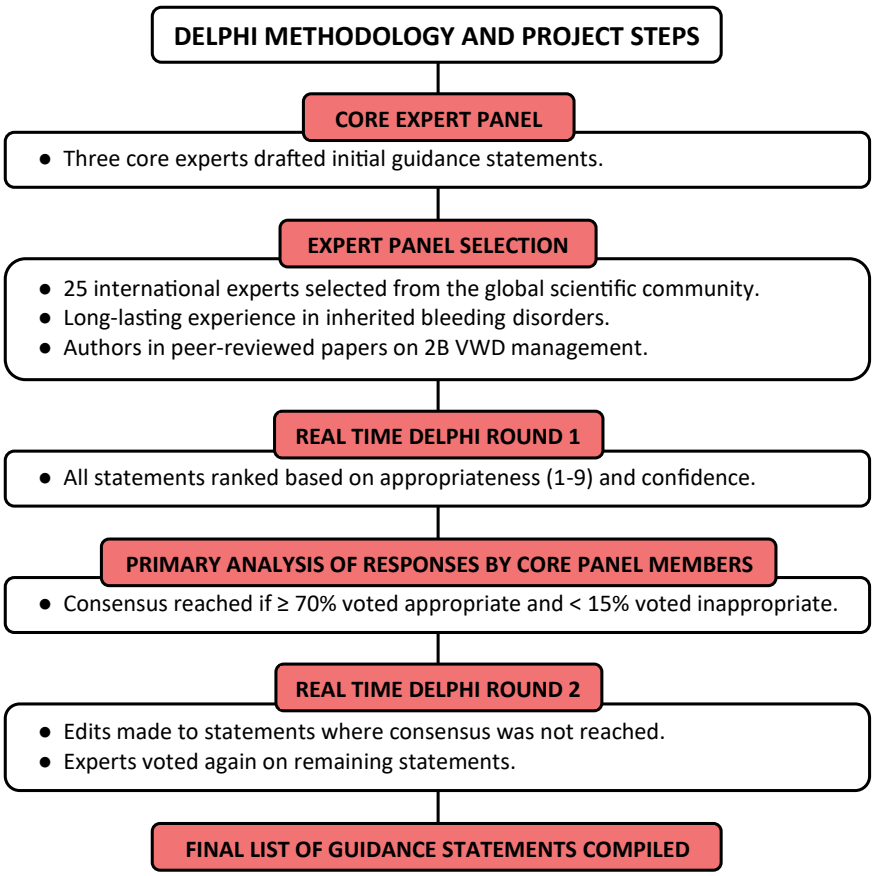

FIGURE 1 Overview of the real-time Delphi methodology and the steps of the project: 14 of 25 experts fully responded. VWD, von Willebrand disease.

United Kingdom, Brazil, Serbia, and Italy. The consensus for the proposed statement was achieved when at least 10 of 14 experts voted in favor of it, with ≤2 voting against.

Following the first round, consensus was achieved for 19 statements. One statement, "If the fetus is known to be affected via prenatal diagnosis, a planned cesarean section may be preferred, especially if there are added obstetric risk factors," did not reach consensus (28.6% of participants rated this as inappropriate and 42.9% as uncertain). Thus, it was excluded from the survey, and consensus was undetermined for 6 statements. The percentage ratings of each statement following the first round with acceptance threshold is shown in Supplementary Figure S1A–C. The numerical details for this round are provided in Supplementary Table S1A.

The 6 undetermined statements were revised based on participants' comments and were disseminated for reassessment in the second round. Following that second round, all 6 revised statements achieved consensus. The percentage ratings assessing of each of those 6 statements following the second round is shown in Supplementary Figure S1D. The numerical details for this round are provided in Supplementary Table S1B.

Overall, of the 26 proposed statements, full consensus was reached for 25 after 2 rounds of voting in the RTD survey. These statements are categorized into 3 themes as follows—theme 1: diagnosis and prenatal counseling (6 statements; Supplementary Table S2A); theme 2: monitoring and management during pregnancy (4 statements; Supplementary Table S2B); and theme 3: management of delivery and postpartum care (15 statements; Supplementary Table S2C).

3.1 | Strength of recommendations

We used the term "we suggest" for statements in which expert consensus was achieved, but the recommendations were informed by lower-quality clinical studies with lower certainty of evidence or by expert opinions. For consensus statements in which recommendations were informed by recent international guidelines on the diagnosis and management of VWD, we used the term "we advise." The statements were not graded according to the balance between benefit and harm, resource implications, and equity considerations due to limited evidence and wide variations in resources across the globe, which may result in unreliable estimations of these categories.

4 | GUIDANCE STATEMENTS, RATIONALE, AND EVIDENCE

This section outlines 25 guidance statements on the management of women with type 2B VWD during pregnancy and postpartum, derived from the 3 primary themes, with a discussion of the rationale and evidence base behind each.

4.1 | Theme 1: diagnosis and prenatal counseling

- Guidance statement 1.1:

In girls and women with abnormal initial VWF tests suggestive of type 2B VWD, we advise that the diagnosis to be established as recommended by American Society of Hematology (ASH)/ISTH/National Hemophilia Foundation (NHF)/World Federation of Hemophilia (WFH) 2021 guidelines, ideally before becoming pregnant.

Evidence and rationale for guidance statement 1.1:

Diagnosing type 2B VWD can be challenging, and a significant delay in the correct recognition of this condition has been underscored in a recent study [20]. Ristocetin-induced platelet agglutination (RIPA) is a hallmark of type 2B VWD diagnosis, but this test has limitations such as poor applicability, technical challenges, and variability in ristocetin sources, which can affect results [27,28].

The 2021 ASH/ISTH/NHF/WFH guidelines on VWD diagnosis recommend genetic testing over RIPA when type 2B VWD is suspected, particularly when VWF:RCo/VWF:Ag ratio is low (<0.7) [29]. In cases where genetic testing is unavailable, RIPA should be performed by laboratory staff with expertise in diagnosing hemostasis disorders [28].

- Guidance statement 1.2:

We suggest that type 2B VWD should be considered as a differential diagnosis in all pregnant women with unexplained and progressive thrombocytopenia.

Evidence and rationale for guidance statement 1.2:

Progressive thrombocytopenia in pregnancy may be the presenting manifestation of type 2B VWD. Therefore, some experts recommend including type 2B VWD in the differential diagnosis of unexplained thrombocytopenia during pregnancy, especially in women with a personal or family history of bleeding disorders [30,31]. Measurement of VWF activity and VWF activity/VWF:Ag ratio can help in differentiation from other more prevalent forms of thrombocytopenia in pregnancy such as gestational and immune thrombocytopenia [29].

- Guidance statement 1.3:

In women presenting during pregnancy with suspected type 2B VWD, we advise that the threshold to perform genetic testing may be lower than in the nonpregnant state to minimize misdiagnosis due to pregnancy-induced changes of hemostatic parameters.

Evidence and rationale for guidance statement 1.3:

Diagnosis of type 2B VWD may be particularly challenging when it is suspected in a pregnant woman. Diagnostic RIPA may not be reliably used during pregnancy due to thrombocytopenia, physiological increase in platelet activation, and platelet adhesion [32,33]. On the contrary, genotyping is not influenced by pregnancy-induced changes in the hemostatic system, and it can also reliably distinguish type 2B VWD from platelet-type VWD. This differentiation is essential since platelet-type VWD is a phenocopy of type 2B VWD, but it is not responsive to VWF replacement therapy [34]. It is also reported that some of the VWF A1 domain variants are associated with predictable changes in VWF multimers and platelet count during pregnancy [5,9].

- Guidance statement 1.4:

We advise appropriate prenatal counseling by a multidisciplinary team (MDT) expert in VWD. Women should be informed about the inheritance pattern of the condition, risk of bleeding during pregnancy, delivery and postpartum, and the need for regular monitoring, and treatment.

Evidence and rationale for guidance statement 1.4:

Reproductive counseling is recommended for women with VWD who are planning pregnancy, as these women face unique risks during pregnancy and postpartum [31]. Despite its distinct clinical and laboratory phenotype, recent guidelines do not provide separate recommendations for type 2B VWD regarding counseling before and during pregnancy. Specifically, type 2B VWD is associated with a high risk of bleeding during delivery and postpartum, a significant potential for development of severe thrombocytopenia requiring platelet transfusions, and specific issues related to the risks for the baby and management of the disease in the neonatal period [20,21,35].

- Guidance statement 1.5:

We suggest that, in women with type 2B VWD, hemoglobin and ferritin levels be checked regularly before and during pregnancy. Iron substitution must be introduced—when indicated—to avoid iron deficiency and/or anemia during pregnancy.

Evidence and rationale for guidance statement 1.5:

Women with VWD are at increased risk of iron deficiency anemia secondary to heavy menstrual bleeding. Regular monitoring of iron

status and correction of iron deficiency before and during pregnancy is recommended by the experts to reduce the risks of maternal and neonatal complications [36]. The presence of iron-deficiency anemia increases risk of primary PPH. In a cohort study of 506 women with VWD, 28% of those who experienced excessive postpartum bleeding had anemia antenatally [37]. The prevalence of iron-deficient anemia in women with type 2B VWD is not known. However, given the more severe bleeding phenotype compared with that in women with type 1 VWD, a similar or higher rate can be expected [13,22].

- Guidance statement 1.6:

We suggest that all women with type 2B VWD are *a priori* at high risk of bleeding during pregnancy and postpartum, irrespective of a bleeding history.

Evidence and rationale for guidance statement 1.6:

It is recognized that women with type 2B VWD are at high risk of bleeding, especially during parturition and postpartum [20,22,23]. Clinical and laboratory phenotype exposed before pregnancy is not a reliable predictor of bleeding during pregnancy or postpartum because women with mild phenotype may also develop serious bleeding complications [38]. Due to extreme phenotypic heterogeneity and lack of methods to stratify the risk of bleeding, experts recommend awareness—among health care professionals—of the bleeding and careful planning of measures to mitigate risk of bleeding during pregnancy and delivery in all women with type 2B VWD [10,39].

4.2 | Theme 2: monitoring and management during pregnancy

- Guidance statement 2.1:

When assessing bleeding risk, we suggest that laboratory test results should not to be evaluated individually. Combined low VWF levels and thrombocytopenia represents a higher risk than each alone. Thrombocytopathy, reported in association with some 2BVWD variants, adds to the risk.

Evidence and rationale for guidance statement 2.1:

Pathogenesis of bleeding complications during pregnancy and postpartum in women with type 2B VWD is multifactorial and includes loss of HMW multimers of VWF, progressive fall of platelet count and platelet dysfunction due to occupation of GPIb receptors by abnormal soluble VWF [10,39]. Separate assessment of VWF levels and platelets count do not provide direct or accurate insight of bleeding tendency because of complex functional defect that defines type 2B VWD [39,40]. When managing women with type 2B during pregnancy, it is suggested that simultaneous monitoring of VWF parameters and platelet function, together with careful clinical assessment, may provide better insight into bleeding risk than focusing on values of individual hemostatic parameters [39].

- Guidance statement 2.2:

We suggest that plasma VWF and FVIII levels and platelet count should be monitored at the beginning of the pregnancy, at least once during the third trimester, close to delivery, and at least once in the first week after delivery. The frequency and timing of testing may be adapted as per clinical judgment.

Evidence and rationale for guidance statement 2.2:

Current guidelines do not specifically address monitoring patterns for type 2B VWD during pregnancy [41,42]. The 2017 Royal College of Obstetricians and Gynecologists (RCOG) and the United Kingdom Doctors' Haemophilia Organisation (UKHCDO) guidelines recommend monitoring VWF activity, VWF:Ag, and factor (F)VIII levels upon admission, in the third trimester, and before invasive procedures in all women with VWD [41]. However, due to the unpredictable changes of platelet count in type 2B VWD, and variable levels of VWF, some experts underscore that regular monitoring of these parameters close to delivery is crucial to help predict the need for replacement therapy and optimize delivery planning [22,43].

- Guidance statement 2.3:

Due to the complexity of type 2B VWD and the high risk of pregnancy-related bleeding events, we advise that labor and delivery should be managed by a, MDT, in a specialized center with access to factor concentrates and blood products, including platelets. It is important to ensure that hemostasis advice and appropriate laboratory monitoring is readily available to the obstetric team.

Evidence and rationale for guidance statement 2.3:

The 2017 RCOG and UKHCDO guidelines recommend that women with types 3 and 2 VWD, including 2B VWD, to be referred for prenatal care and delivery in a maternity unit with a specialist in high-risk obstetrics and affiliated with a hemophilia treatment center where all necessary expertise and resources required for laboratory monitoring and treatment can be timely provided [41]. Experts also emphasize that communication and collaboration of the MDT members contribute to the successful management of women with high-risk VWD during pregnancy and postpartum [44].

- Guidance statement 2.4:

We suggest that in women with type 2B VWD who experienced bleeding requiring VWF replacement therapy during pregnancy, subsequent prophylactic administration of VWF concentrate may be considered. The dosing, intervals of administration, and duration of prophylaxis are determined based on bleeding risk, clinical response, and VWF/FVIII levels.

Evidence and rationale for guidance statement 2.4:

In cases of bleeding or the need for invasive procedures during pregnancy, careful consideration must be given to the clinical and laboratory findings, as platelet counts may decrease during bleeding episodes or invasive procedures due to the abnormal VWF release induced by the bleeding [10]. While some authors suggest that VWF concentrate prophylaxis may be considered in the prevention of antenatal bleeding in women with low VWF levels, data on its effectiveness for prolonged use during pregnancy are limited [22]. However, the potential harm of significant bleeding may justify its use in high-risk cases [22].

4.3 | Theme 3: management of delivery and postpartum care

- Guidance statement 3.1:

We advise that a delivery plan should be formulated in the third trimester using a shared decision-making process with the patient and MTD members. If any changes in the delivery plan are required, it is essential that these are discussed with the patient, clearly documented, and communicated to all the MTD members.

Evidence and rationale for guidance statement 3.1:

The 2006 UKHCDO guidelines recommend that a delivery plan be formulated ahead of expected date of delivery by an MDT consisting of hemostasis experts, high-risk obstetrics, anesthesiology, pharmacy, neonatology, blood bank, and an expert coagulation laboratory [45]. The plan must contain details related to the mode of delivery, laboratory monitoring, and hemostatic cover in the peripartum period, pain control and anesthesia, and management of the mother and the baby during labor and delivery. The mother must be familiar with the plan and agree to it, and the plan must be communicated to all involved in the circle of care [46].

- Guidance statement 3.2:

We suggest that the mode of delivery mostly depends on obstetric indications. Delivery must be achieved with the least traumatic method to the baby, avoiding fetal blood sampling, fetal scalp monitoring, ventouse delivery, and midcavity forceps. We also advise avoidance of external cephalic version during pregnancy for breech presentation.

Evidence and rationale for guidance statement 3.2:

In the recent guidelines, it is recommended that the mode of delivery in women with VWD must be guided by obstetric indications, providing the least traumatic method to the mother and the baby [41,42]. However, despite the peculiar pathophysiology and high bleeding risk, mode of delivery in type 2B VWD is not specifically addressed in these guidelines. Analysis of aggregated data from a systematic review of the literature and from an international registry on 43 pregnancies in women with type 2B VWD showed that 70% pregnancies ended as cesarean section and 30% as vaginal delivery [20]. Higher preference of obstetricians for cesarean section in this study may reflect uncertainty related to the estimated risk of bleeding in neonates born by vaginal delivery and anticipated complexity of hemostatic treatment in the peripartum period [20]. The RCOG stratified the risk of bleeding in neonates potentially affected with different VWD types and recommend that instrumental vaginal delivery be avoided and special precautions must be implemented to minimize hemorrhagic risk in neonates at risk of having type 2 and 3 VWD [41]. It must be noted that hemorrhagic risk may be particularly elevated in infants with type 2B VWD who have low platelet count and in affected low birthweight preterm neonates ($\leq$32 gestations' weeks), because of increased expression of GPIbα receptors on the surface of their platelets [47,48].

- Guidance statement 3.3:

We suggest that VWF-containing concentrate and blood products should be readily available during pregnancy, at the time of delivery, and postpartum for all women with 2B VWD.

Evidence and rationale for guidance statement 3.3:

Women with type 2B VWD are at increased risk of pregnancy-associated hemorrhagic complications, especially PPH [20,23]. Antepartum hemorrhage is not common in women with VWD but may occur because of miscarriage, invasive procedures, or spontaneously due to hemostatic defects or gynecologic problems [31]. Based on the high risk of bleeding and complex coagulation defect in women with type 2B VWD, experts emphasize that close hemostatic monitoring during pregnancy and postpartum must be ensured and that clotting factor concentrates and blood products, including platelets, must be readily available [46].

- Guidance statement 3.4:

The safe level of VWF and platelet count for neuraxial anesthesia in women with type 2B VWD is not known, and we suggest that the

risk must be assessed individually. Intervention must be avoided if the VWF activity level is <50 IU/dL and/or platelet count <70 × 10^9/L. The trough levels of VWF activity during neuraxial catheter stay must be >50 IU/dL. The removal of the catheter needs approximately the same levels of VWF and platelet count as for its placement.

Evidence and rationale for guidance statement 3.4:

There is controversy regarding the safety of neuraxial anesthesia in women with type 2B VWD. Some experts recommend against it, while others report successful anesthesia in these patients [49,50]. Current guidelines suggest a target VWF in the range of 50 to 150 IU/dL [42,51]. The safe platelet count is not known, but a target of ≥70 × 10^9/L has been suggested for women with immune thrombocytopenia [52]. In women with type 2B VWD and low platelet count, it may be difficult to achieve this threshold with platelet transfusions in a short timeframe. This must be considered when evaluating for neuraxial anesthesia, particularly outside planned delivery or in urgent obstetric situations.

- Guidance statement 3.5:

We advise that DDAVP to be avoided in women with type 2B VWD during pregnancy and postpartum due to the risk of causing/worsening thrombocytopenia.

Evidence and rationale for guidance statement 3.5:

Although DDAVP is recommended and widely used in type 1 VWD, its use is contraindicated in patient with type 2B VWD due to risk of provoking or worsening of thrombocytopenia and exacerbating the risk of bleeding [42,53].

- Guidance statement 3.6:

We suggest that both laboratory results and clinical scenarios must guide replacement therapy with VWF, FVIII, and platelets for delivery and postpartum.

Evidence and rationale for guidance statement 3.6:

Close monitoring of VWF levels and platelet count is recommended in women with type 2B VWD receiving VWF replacement therapy and/or platelet transfusion in the peripartum period [43]. However, in the recent study, clinically significant bleeding was recorded in 24% of pregnancies in women with type 2B VWD treated with VWF replacement therapy [20]. Because of the variable response to hemostatic treatment in women with type 2 and 3 VWD, some experts emphasize that effects of therapy be carefully evaluated, and in the case of unsatisfactory bleeding control, the patient must be individually assessed by an MDT with expertise in VWD [46].

- Guidance statement 3.7:

We suggest that the targeted VWF activity and FVIII levels for delivery are ≥100 IU/dL. Trough VWF/FVIII level should be kept at ≥80 IU/dL during the first 3 to 5 days after vaginal delivery and during 5 to 7 days after cesarean section. Replacement therapy could be continued beyond this period if excessive bleeding or a significant risk of bleeding persists with an adjustment of treatment according to clinical circumstances.

Evidence and rationale for guidance statement 3.7:

Due to a lack of high-quality data in the literature, there is no consensus on the safe levels of VWF and FVIII for delivery in women with VWD. The 2017 RCOG guidelines recommend VWF replacement therapy if VWF levels are <50 IU/dL before delivery, aiming for peak levels of 100 IU/dL and trough levels of 50 IU/dL [41]. However, despite following these guidelines, PPH remains common [54,55].

The recent ASH/ISTH/NHF/WFH guidelines suggest aiming for VWF levels of >150 IU/dL in some cases to avoid PPH, and the Netherlands' national guidelines now recommend attaining VWF activity (VWF:RCo) levels of >150 IU/dL at the time of delivery in women with prepartum VWF levels of <80 IU/dL [42,56]. In women with type 2B VWD, the threshold for VWF replacement therapy may also need to be higher than previously recommended, as lower VWF levels may not adequately prevent peripartum bleeding [20,57].

- Guidance statement 3.8:

We suggest that platelet transfusion be administered when the platelet count is <30 × 10^9/L at the start of vaginal delivery or <50 × 10^9/L in case of cesarean delivery. Repeated platelet transfusions may be needed to achieve counts >30 × 10^9/L during the first 3 to 5 days after delivery.

Evidence and rationale for guidance statement 3.8:

Significant thrombocytopenia is common in women with type 2B VWD during pregnancy. In a recent study of 42 pregnancies, third-trimester platelet counts of <50 × 10^9/L and <20 × 10^9/L was reported in 55% and 26% of women, respectively [20]. Federici et al. [10] have reported that thrombocytopenia is an independent risk factor for bleeding in patients with type 2B VWD.

Some authors have questioned the effectiveness of platelet transfusion in women with type 2B VWD because of reported poor recovery or platelet clumping [58,59].

However, both current guidelines and experts point out that platelet transfusions may be necessary in some situations, although the exact threshold for transfusion is not well defined due to a lack of high-quality evidence [39,43]. Current recommendations target platelet counts of $\geq 20 \times 10^9$/L for vaginal delivery and $\geq 50 \times 10^9$/L for cesarean sections [39,45], while results from the recent study suggest these thresholds may be too low to prevent peripartum bleeding complications [20]. Figure 2 shows proposed practical guidance for hemostatic coverage at the time of delivery in women with type 2B VWD.

- Guidance statement 3.9:

If there is excessive bleeding during delivery or postpartum despite correct VWF replacement, we suggest that platelet transfusion be administered to achieve a platelet count $>50 \times 10^9$/L.

Evidence and rationale for guidance statement 3.9:

In addition to low platelet count, platelet dysfunction caused by 2B VWF variant may contribute to hemorrhagic potential [60]. RCOG guidelines recommend that platelet transfusion may be needed in some women with type 2B VWD, but the target platelet count that must be achieved in case of excessive bleeding is not defined [41]. In the recent study, 61% of deliveries in women with type 2B VWD and platelet count $<50 \times 10^9$/L were complicated by PPH, despite receiving VWF replacement therapy [20]. The platelet count at delivery $>50 \times 10^9$/L is recommended in women with immune thrombocytopenia, indicating that a lower platelet count could be insufficient to provide effective hemostasis when an intense hemostatic challenge is present [52].

- Guidance statement 3.10:

We suggest that blood count, plasma VWF activity, and FVIII levels should be checked at least once in the first 24 hours after delivery in all women with type 2B VWD. In women receiving VWF and/or platelet replacement therapy, levels must be regularly monitored during the entire treatment period.

Evidence and rationale for guidance statement 3.10:

In pregnant women with type 2B VWD, thrombocytopenia may vary from mild to severe, and the nadir of platelet counts is usually observed during the first postpartum day, while VWF:RCo levels commonly remain subnormal [22,39].

Due to unpredictable changes in the VWF activity levels and platelet count in the last days of pregnancy and during the first few days after delivery, experts recommend close clinical surveillance and laboratory monitoring of all women with type 2B VWD during pregnancy, in the early postpartum period, and during the entire period of treatment with VWF and/or platelet replacement therapy [39].

- Guidance statement 3.11:

We suggest that women with type 2B VWD undergo individualized venous thromboembolism (VTE) risk assessment. If pharmacologic thromboprophylaxis is indicated, it should be administered for the minimum necessary duration, with close clinical surveillance and appropriate laboratory monitoring of hemostatic parameters.

Evidence and rationale for guidance statement 3.11:

Pregnancy and the postpartum period are associated with increased risk of VTE. In a large cohort study, women with VWD experienced a similar risk of pulmonary thromboembolism as women without VWD after childbirth [61].

According to recent UK guidelines, low-molecular-weight heparin may be recommended for prophylaxis of pregnancy-associated venous thrombosis in inpatients with VWD, provided that levels of VWF:RCo and FVIII are corrected [41].

Due to the frequent occurrence of postpartum hemorrhage in women with type 2B VWD, a cautious and individualized approach for administration of pharmacologic thromboprophylaxis is suggested [22]. The nonpharmacologic methods of thromboprophylaxis, including early mobilization, antiembolism compression stockings, and intermittent pneumatic compression device are less efficacious, but they are not associated with hemorrhagic risk [22]. Therefore, nonpharmacologic methods should be considered the preferred first-line strategy for prophylaxis of pregnancy-associated VTE in women with type 2B VWD.

- Guidance statement 3.12:

We advise the use of postpartum tranexamic acid according to the ASH/ISTH/NHF/WFH 2021 guidelines, which favor administration of tranexamic acid over not. Tranexamic acid may be given via the oral or intravenous route. The recommended oral dose is ~25 mg/kg 3 times per day for 10 to 14 days or longer if blood loss remains heavy. Women who intend to breastfeed should be provided education about benefits and the safety of tranexamic acid during breastfeeding.

Evidence and rationale for guidance statement 3.12:

There is increased local and systemic fibrinolytic activity after childbirth, contributing to the risk of bleeding. Administration of tranexamic acid at delivery and postpartum aim to inhibit fibrinolysis, decreasing blood loss, and reducing mortality caused by PPH [62].

Recent ASH/ISTH/NHF/WFH guidelines support its use for women with types 1, 2, and 3 VWD [42], with the understanding that it is safe during breastfeeding [63].

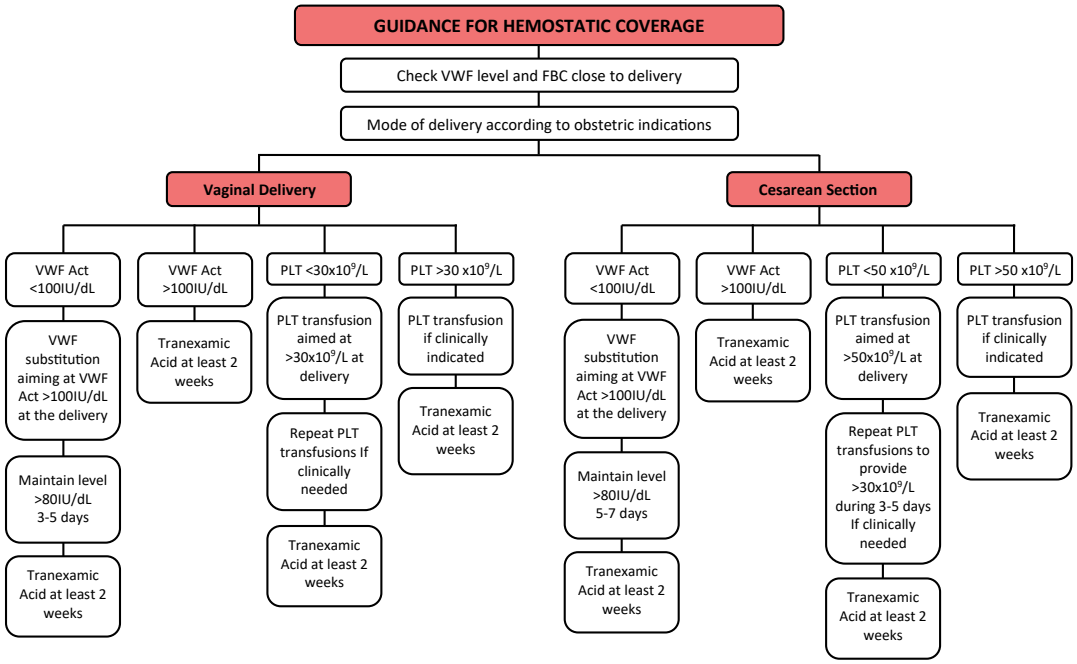

FIGURE 2 Proposed practical guidance for hemostatic coverage at the time of delivery in women with type 2B VWD. FBC, full blood count; PLT, platelet; VWD, von Willebrand disease.

- Guidance statement 3.13:

In cases of excessive postpartum bleeding, we suggest immediate, concurrent hemostatic and obstetric assessment. Hemostatic therapy should be guided by bleeding phenotype and laboratory results, while obstetric evaluation should identify and manage obstetric causes of hemorrhage.

Evidence and rationale for guidance statement 3.13:

Excessive postpartum bleeding in women with type 2B VWD requires urgent clinical and laboratory evaluation of hemostasis, especially if the cause of hemorrhage is unclear [64]. In addition to low VWF levels and thrombocytopenia, other inherited or acquired abnormalities of hemostasis, including acquired inhibitors of clotting factors, may be behind excessive bleeding in women with type 2B VWD during pregnancy and postpartum [64]. Obstetric factors may also cause excessive or prolonged postpartum bleeding, and its occurrence requires urgent obstetric assessment to rule out obstetric causes of hemorrhage [46].

- Guidance statement 3.14:

After discharge, we advise that the team should keep close contact with the patient until the resolution of lochia. In case of significant bleeding, the patient will need an immediate assessment at the obstetric and hemostasis centers undergoing to rule out/manage obstetric causes for bleeding.

Evidence and rationale for guidance statement 3.14:

In women with VWD, PPH may occur several days or even weeks after delivery, and it is reported that the mean timing of occurrence of PPH was 15.7 ± 5.2 days after childbirth [65]. In RCOG guidelines, it is recommended that women with VWD must be made aware of the risk and encouraged to immediately report any occurrence of excessive bleeding postpartum. It is also recommended that contact with them must be maintained for several weeks after delivery [41]. Regular visits by a hemophilia nurse and a community midwife are an efficient way to keep close contact with the patient during the increased risk of postpartum bleeding [46].

- Guidance statement 3.15:

If prenatal testing is not done, we suggest that screening for type 2B VWD in the neonate may be done using cord blood sampling. Until the diagnosis of type 2B VWD is excluded, vaccines must be given subcutaneously with the smallest gauge needle. Vitamin K should be given orally if there is a delay in the diagnosis or the diagnosis of type 2B VWD is confirmed. The drug may also be administered subcutaneously if appropriate formulation is available and approved.

Evidence and rationale for guidance statement 3.15:

Umbilical cord blood VWF levels are not reliable for confirming a diagnosis of type 2B VWD, but they can be used to assess bleeding risk in neonates from VWD-affected mothers [66]. Until bleeding disorders are ruled out, invasive procedures like intramuscular vitamin K injections must be avoided, and vaccines must be administered subcutaneously [45]. However, some authors suggest that immunization and vitamin K may be administered through the usual route using a small-gauge needle, applying pressure and ice to the area if the neonate is known to be affected with 2B VWD [38]. The Guthrie test (heel prick test), a neonatal screening for common inborn errors of metabolism, can be safely performed by applying gentle pressure to the puncture site for 5 minutes immediately after the sample is collected [67].

5 | CONCLUSION

Given the lack of high-level evidence, the RTD method was used to establish formal consensus among 14 international experts on the diagnosis, monitoring, and treatment of women with type 2B VWD during pregnancy and postpartum. This project was conducted as a collaborative effort between the ISTH Scientific Committees on VWF and the ISTH Subcommittee on Women's Health Issues in Thrombosis and Hemostasis. Following 2 rounds of anonymous voting and subsequent refinements, consensus was achieved on 25 statements, which now form the foundation of this guidance document. These statements provide a robust framework to standardize management practices and enhance clinical outcomes for this patient population.

AUTHORS CONTRIBUTIONS

P.M., M.L., R.A.-K., P.J., and M.O. designed the project. A.N. administered the RTD survey and analyzed data. P.M. and M.O. analyzed and interpreted data. P.M., A.N., and M.O. wrote the first draft. A.S.-L., R.B., R.S., and P.J. are members of the expert core group and contributed intellectually to the project, guided the construction of the guidance statements, and critically reviewed the manuscript.

DECLARATION OF COMPETING INTEREST

There are no competing interests to disclose.

DRAFT STATEMENT ON CONFLICT MANAGEMENT DURING THE DEVELOPMENT OF INTERNATIONAL GUIDANCE

During the development of this international guidance, the core group and expert panel used the Delphi method to ensure a structured, iterative, and consensus-driven approach. To maintain the integrity and credibility of the guidance, all potential conflicts of interest among panel members were identified and disclosed at the outset of the process. Conflicts were managed through the following measures:

Disclosure: Panel members provided full disclosure of any professional, financial, or personal interests relevant to the subject matter.

Recusal when necessary: Members with identified conflicts were recused from specific rounds of discussion or decision making where their impartiality might be compromised.

Transparency: A record of disclosed conflicts and the steps taken to mitigate them was maintained are made available.

These steps were implemented to ensure that the guidance reflects a balanced and unbiased consensus, grounded in evidence and expert judgment.

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SUPPLEMENTARY MATERIAL

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