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ORIGINAL ARTICLE

Examining international practices in the management of pregnant women with von Willebrand disease

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Abstract

Background: The management of pregnant women with von Willebrand disease (VWD) is complex as physiological pregnancy-induced increases in plasma von Willebrand factor (VWF) may be blunted or absent. Women with VWD experience a heightened risk of postpartum hemorrhage (PPH) and special consideration must be given regarding neuraxial anesthesia (NA) and the need for prophylaxis at time of delivery. These challenges are compounded by a lack of robust evidence to guide clinical decision-making.

Objectives and Methods: To determine the current international clinical practices in the management of pregnancy for women with VWD, the International Society on

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Thrombosis and Haemostasis (ISTH) conducted an international survey of health-care providers (HCP).

Results: One hundred thirty-two respondents from 39 countries were included in the final analysis. Variations in clinical practice were identified in antenatal (monitoring of plasma VWF and ferritin levels), peripartum (optimal plasma VWF target at delivery) and postpartum management (definitions used for PPH and postpartum monitoring). A key area of divergence was suitability for NA for women with type 2 and type 3 VWD, with many respondents advising against the use of NA even with VWF supplementation (29% type 2 VWD, 37% type 3 VWD) but others advising use once plasma VWF activity was >50 IU/dL (57% type 2 VWD; 50% type 3 VWD).

Conclusions: This survey highlighted areas of uncertainty surrounding common management issues for pregnant women with VWD. These data underscore the need for international collaborative research efforts focused on peripartum management to improve care for pregnant women with VWD.

KEYWORDS

anesthesia, postpartum, pregnancy, von Willebrand disease, von Willebrand factor

1 | INTRODUCTION

von Willebrand disease (VWD) is a bleeding diathesis resulting from a quantitative or qualitative deficiency in von Willebrand factor (VWF). VWF is a critical coagulation protein, serving to juxtapose platelets to exposed subendothelial collagen at sites of vascular injury. VWD is one of the most common bleeding disorders worldwide, with reduced plasma VWF levels and a bleeding phenotype present in 1/1000 people.[1] The bleeding phenotype associated with VWD is mucocutaneous in nature with epistaxis, easy bruising, and gynecological bleeding frequently reported. In contrast to hemophilia, VWD is autosomally inherited; however, women are more likely to seek assessment and be diagnosed due to heavy menstrual bleeding (HMB).[2] Excess gynecological bleeding is significantly increased in women with VWD compared to the general population, with HMB rates of up to 90% reported[2–5] and postpartum hemorrhage (PPH) rates ranging widely from 6–50%, depending on the sample size and severity of VWD studied.[6] Childbirth represents a major hemostatic challenge for women with VWD who, compared to pregnant controls, are 1.5 times more likely to develop a PPH, with a higher risk of both transfusion (5-fold) and death (10-fold).[7] Indeed, the occurrence of severe PPH may prompt consideration of hemostatic testing, serving as the diagnostic bleeding event for many women with VWD.[8] Following childbirth the risk of excess bleeding persists, with higher reported rates of secondary PPH (excess bleeding >24 h to 6 weeks following delivery) of up to 30% compared to 2% in the general population.[6]

The clinical management of pregnant women with VWD involves both patient preference and the combined clinical input of the obstetrics, anesthetics, and hemophilia treatment center (HTC) teams. Pregnancy is one of the most complex hemostatic challenges that women with VWD experience, not only due to considerations of maternal and fetal risk but also the concomitant physiological alterations in coagulation. Plasma VWF levels in pregnant women start to rise early in pregnancy, ultimately increasing 2- to 3-fold from baseline.[9,10] For women with VWD, this pregnancy-induced change may be absent or blunted.[9] In women with VWD who experience a rise in plasma VWF levels, the trajectory of increase parallels healthy pregnant peers but remains lower at all timepoints.[9] This introduces uncertainty regarding plasma VWF therapeutic targets peripartum and duration of treatment. The clinical impact of these issues is clear, with elevated rates of primary PPH in women with VWD despite prophylactic therapy at the time of delivery.[9,11,12] Large clinical trials to optimize care for pregnant women with VWD are lacking and management is largely based on expert-based consensus guidelines.[13,14] To assess current clinical practice in the management of pregnant women with VWD, we developed a clinician survey

ESSENTIALS

- Limited published evidence exists regarding the management of pregnant women with von Willebrand disease.
- We undertook a global survey of clinical practices to identify areas of uncertainty or divergence.
- Significant variations in clinical practice exist, especially with respect to neuraxial anesthesia.
- The optimal plasma von Willebrand factor therapeutic targets or treatment approaches for delivery remain unclear.

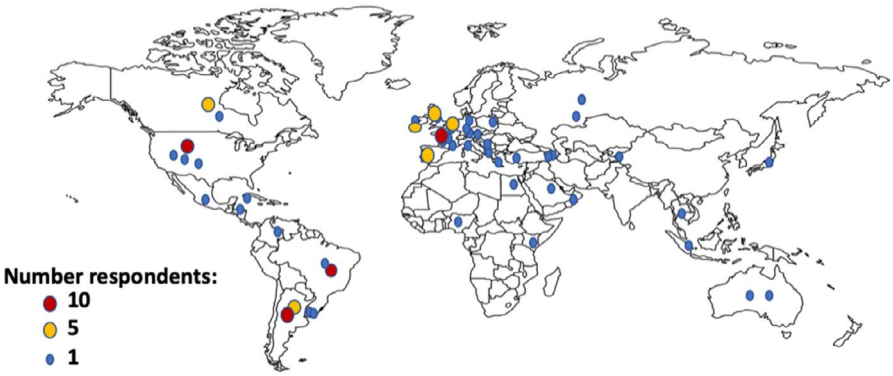

FIGURE 1 Geographical distribution of survey respondents: 10 participants indicated by red dot, 5 by yellow, single participant by blue dot

using the platform of the International Society on Thrombosis and Haemostasis (ISTH), which was disseminated internationally to provide an insight into global practices in the management of women with VWD. Through this method, we aimed to highlight areas of uncertainty and divergence in practice to provide a roadmap for future research.

2 | METHODS

Prior to development of the survey, this project was endorsed by both the VWF and Women's Health Scientific and Standardization Committees (SSC) at the 2018 Annual ISTH SSC meeting in Dublin. The text of the survey was designed between July and October 2018 (Appendix S1 in supporting information) and transferred to the Research Electronic Data Capture (REDCap) platform. Study data were collected and managed using REDCap electronic data capture tools hosted at ISTH.[15,16] Content, language, and usability were tested on the members of both the VWF and Women's Health SSCs prior to launch. Once approved, the survey was translated into Spanish (Appendix S2 in supporting information) to increase global access. Dissemination was achieved via ISTH mailing lists and a social media campaign. All clinicians involved in the care of women with VWD during pregnancy were eligible to respond. The survey remained open from October 24, 2018 to March 16, 2019. Respondents were asked a series of 19 questions, covering preferred treatment options for women with VWD, plasma VWF thresholds, use of bleeding assessment tools (BATs), targets of therapy, advice regarding neuraxial anesthesia, and management in the postpartum period.

Survey responses that were deemed incomplete (<5 answers or demographics only) were excluded from the study. From the remaining eligible responses, results were collated and analyzed. If all respondents did not answer a specific question, the number of responses for that question are reported. Basic demographics, practice location, size, and speciality of each user were captured to provide context to the clinical practices described. Assays of VWF function (e.g., VWF ristocetin co-factor, VWF:RCo; VWF glycoprotein Ib, VWF:GpIb; and VWF collagen binding assays, VWF:CB) are collectively referred to in this article as "VWF:activity" (VWF:Act) for ease of reference. At the time of the survey "low VWF" was used to refer to those women with baseline plasma VWF levels of 30–50 IU/dL with a bleeding phenotype. Descriptive statistics are presented as frequencies and percentages (*n*, %). Statistical analyses were performed using Prism 8 for Mac OSX, Version 8.1.2 (GraphPad).

3 | RESULTS

Overall, 215 unique entries to the survey were recorded. Incomplete responses (fewer than five questions answered or only basic demographics complete) accounted for 73 of the entries. These entries were excluded from subsequent analysis. The final group comprised 132 respondents from 39 countries (21.2% in Spanish; Figure 1). The majority of respondents identified as coagulation specialists (77.3%) with general hematologists accounting for 17.4% and other specialities (obstetricians, general physicians, transfusion specialists) the remaining 5.3%. Most respondents worked in a tertiary (89.4%) rather than secondary (8.3%) or primary (1.5%) care setting. The number of patients with VWD treated in each respondent's center was recorded, with an even distribution of practice sizes seen (<50 patients with VWD in 27.7%, 50–100 in 26.9%, 151–300 in 21.5%, >300 in 23.8%). Overall, 74.2% of respondents use standardized phenotypic assessment with BATs in their clinical practice, but the frequency and consistency of use varied. 75.5% used BATs "regularly" or "always," compared to "infrequent" (11.2%) or "sometimes" (12.2%). The ISTH BAT was the most commonly used tool (70.4%), followed by the Condensed MCMDM-1VWD (Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD) score (21.4%), the Self BAT (13.3%), and the MCMDM-1VWD tool (8.2%) (respondents could choose more than one option if used in their practice).

3.1 | How does VWD impact antenatal monitoring and delivery planning?

While antenatal monitoring of plasma VWF levels is recommended,[13,17,18] the frequency and timing of monitoring may vary among centers.[19] Respondents advised assessment of plasma VWF levels in the third trimester most frequently (94.7%), either alone (28%), in combination with first trimester levels (29.5%), second

trimester (4.5%), in all three trimesters (13.6%), or used another schedule. Of interest, for women with low VWF levels, 43.8% of respondents checked levels once during pregnancy and, if they had increased to within the normal reference range (>50 IU/dL), no further antenatal monitoring was performed.

Pregnancy may induce a consumptive iron deficiency, with anemia a well-established risk factor for PPH.[20] When surveyed, 93% advised evaluation of hemoglobin and/or iron status during pregnancy in women with VWD, often with repeat testing (66% of respondents perform assessment in the first trimester, 28.5% in second trimester, and 64.3% in third trimester). It was noted by some respondents that hemoglobin and iron status is routinely checked at their first antenatal visit and 28 weeks gestation by the local obstetric facility for all pregnant women or that assessment of iron status is restricted to those pregnant women identified to have anemia. Despite the known increased risk of secondary PPH for women with VWD, postpartum iron and hemoglobin checks were less frequently advocated, with only 67.4% of all respondents routinely evaluating these parameters.

For women with bleeding disorders, delivery in a specialist obstetric hospital (i.e., allied with an HTC and/or with an on-site hemostasis lab) may be recommended, but this may be challenging if these centers are geographically distant. VWD subtype influenced the advice to deliver at a specialist center (n = 91), ranging from 30.7% for low VWF, 45.5% for type 1 VWD, increasing to 74.1% for type 2 VWD and 87.1% for type 3 VWD. When asked what mode of delivery is advised for each VWD subtype (n = 102), the majority of respondents advised delivery based on obstetric indications (low VWF = 88%, type 1 VWD = 87%, type 2 VWD = 82.7%, type 3 VWD = 69%, Figure 2A) rather than planned induction/elective lower segment Caesarean section (LSCS). Increased rates of planned induction (17%) or elective LSCS (14%) were advised for women with type 3 VWD, likely related to concerns about bleeding risk (Figure 2A). In addition, comments provided indicated that planned delivery may also be considered in those living distant to obstetric services.

3.2 | Can neuraxial anesthesia be offered to women with VWD at delivery?

Respondents were asked to outline the advice they give regarding suitability for neuraxial anesthesia (NA) for women of each VWD subtype (n = 108). Four options were offered for each subtype: not permissible irrespective of levels, permissible only if both VWF:Ag and VWF:Act >50 IU/dL, if VWF:Act >50 IU/dL, or if VWF:Ag >50 IU/dL (for Type 2B VWD it was assumed platelets >50 x10^9/L and Type 2N factor VIII [FVIII] >50 IU/dL). Marked differences in responses were seen, particularly in relation to lack of suitability for NA irrespective of levels: 29% of respondents for type 2 VWD and 37% for type 3 VWD selected that NA is unsuitable for these women irrespective of levels and supplementation (Figure 2B). This contrasted sharply with respondents who advocated for NA once either the VWF:Ag and VWF:Act or VWF:Act alone was >50 IU/dL (57% type 2 VWD; 50% type 3 VWD; Figure 2B).

We examined whether there was a geographical influence on these divergent responses. Focusing on type 3 VWD, European respondents were more likely to select that women were unsuitable for NA (53.1%, n = 26/49) compared to 34.5% (n = 10/29) of those from South and Central America and only 7.1% (n = 1/14) of North American respondents. Although numbers are limited, these data highlight differing practices internationally and suggest that women with type 3 VWD may be more likely to access NA in North America.

3.3 | What plasma VWF targets and hemostatic cover should be used at time of delivery?

There remains uncertainty as to ideal trough plasma VWF and FVIII levels in the postpartum period. Survey participants (n = 83) were asked what plasma VWF targets are used locally when VWF replacement therapy was required: 80.7% maintained plasma VWF and FVIII levels >50 IU/dL, 15.7% maintain a higher trough of >100 IU/dL, and 3.6% used an alternative approach (peak of >150 IU/dL at delivery, maintaining trough >50 IU/dL thereafter). The most frequently advised durations of treatment were 3–5 days for spontaneous vaginal delivery (SVD, 57.4%) and 5–7 days for a LSCS (60%). Shorter durations or lower troughs (<50 IU/dL) were infrequently selected (8.2% of SVD 11.7% for LSCS). Longer durations of replacement therapy (7–14 days) were recommended by 34.4% of respondents for SVD and 28.3% for LSCS.

As seen in Figure 3A, the use of prophylactic tranexamic acid (TXA) for women with type 2 and type 3 VWD was advised by 47% and 45% of respondents, respectively (n = 85). Similar rates (49%) were seen for women with type 1 VWD with levels <50 IU/dL in the third trimester; however, the lower rates were seen for women with low VWF (29%) and type 1 VWD with levels >100 IU/dL at time of delivery (22%). The presence of a history of PPH influenced the decision to give TXA in many respondents (ranging from 27% with low VWF to 15% with type 3 VWD, Figure 3A), although TXA was often used as adjunctive therapy in type 2 and type 3 VWD compared to low VWF and type 1 VWD (Figure 3A–C). Similar figures across each disease subtype (ranging from 35–37%) reserve TXA for use only if excess bleeding occurs.

Prophylactic DDAVP (desmopressin) was infrequently advised, with highest rates of use selected for women with type 1 VWD whose third trimester levels were <50 IU/dL (Figure 3B). Among those with low VWF and type 1 VWD with levels >50 or >100 IU/dL, DDAVP usage at delivery was predominantly selected for use in the event of bleeding. Unsurprisingly, prophylactic clotting factor concentrate use (CFC, Figure 3C) was the most frequently advised treatment for women with type 2 and type 3 VWD, with comments often suggesting use in combination with TXA.

When VWF replacement therapy was required for peripartum management, plasma-derived VWF (pdVWF) was the most

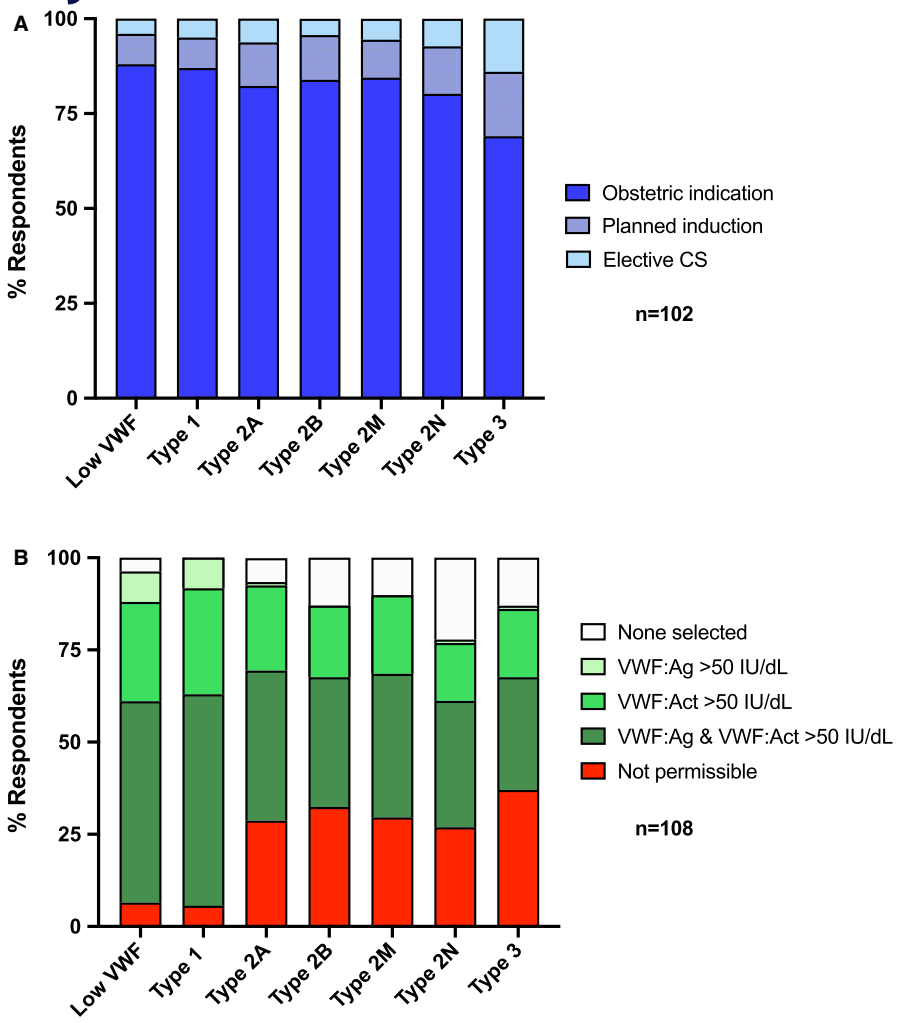

FIGURE 2 Mode of delivery (A) and suitability for neuraxial anesthesia (B) by von Willebrand disease (VWD) subtype. CS, Cesarean section; VWF:Act, von Willebrand factor activity; VWF:Ag, von Willebrand factor antigen

commonly reported source used, comprising 89.5% of responses. Use of recombinant VWF (rVWF) internationally remains limited, likely due to availability and the current product licence, accounting for only 5.8% of responses. For the final 4.7%, cryoprecipitate and fresh frozen plasma remained the only available products for peripartum prophylaxis. The choice of product used was largely dictated by local availability (26.7%) or access to only a single product (24.4%). Another factor that influenced choice of products was composition, with a high VWF:FVIII ratio (29.1%) or minimal FVIII content (15.1%) favored.

3.4 | How is postpartum hemorrhage defined?

Internationally, multiple definitions of primary PPH (within 24 h of delivery) are in use,[21–23] increasing the difficulty of comparative analysis of rates of PPH in studies of pregnant women with VWD. When surveyed on the definition in use in their institution (n = 79), 26.6% of respondents used a threshold of >500 mL blood loss irrespective of mode of delivery, 43% used >500 mL for a vaginal but >1000 mL for a LSCS, 7.6% used >1000 mL irrespective of mode of delivery. Despite the high levels of blood loss required to result in signs of hypovolemia at delivery,[24] this definition remains in use for 22.8% of respondents.

3.5 | How are women with VWD monitored postpartum?

When asked which coagulation assays routinely monitored postpartum women (n = 83) only two respondents selected isolated FVIII monitoring (2.4%). All others use VWF:Act; either in combination with both VWF:Ag and FVIII (71.1%), with only FVIII (19.3%), or in isolation (6%). Despite the advent of novel assays of VWF:Act, the VWF:RCo remains the most frequently used VWF:Act assay (71%), with only 23 respondents describing use of either the VWF:GpIbR, VWF:GpIbM, VWF:Ab, VWF:CB assay, or a combination thereof. All respondents indicated peripartum monitoring is advised; however, significant heterogeneity in the timing and frequency of sampling was seen as indicated in Table 1. Unsurprisingly, intensive sampling (at onset of labor, delivery, and in the first week) was recommended more frequently for type 2 VWD (32.5%) and type 3 VWD (43%) compared to those with type 1 VWD/low VWF levels (16.2%).

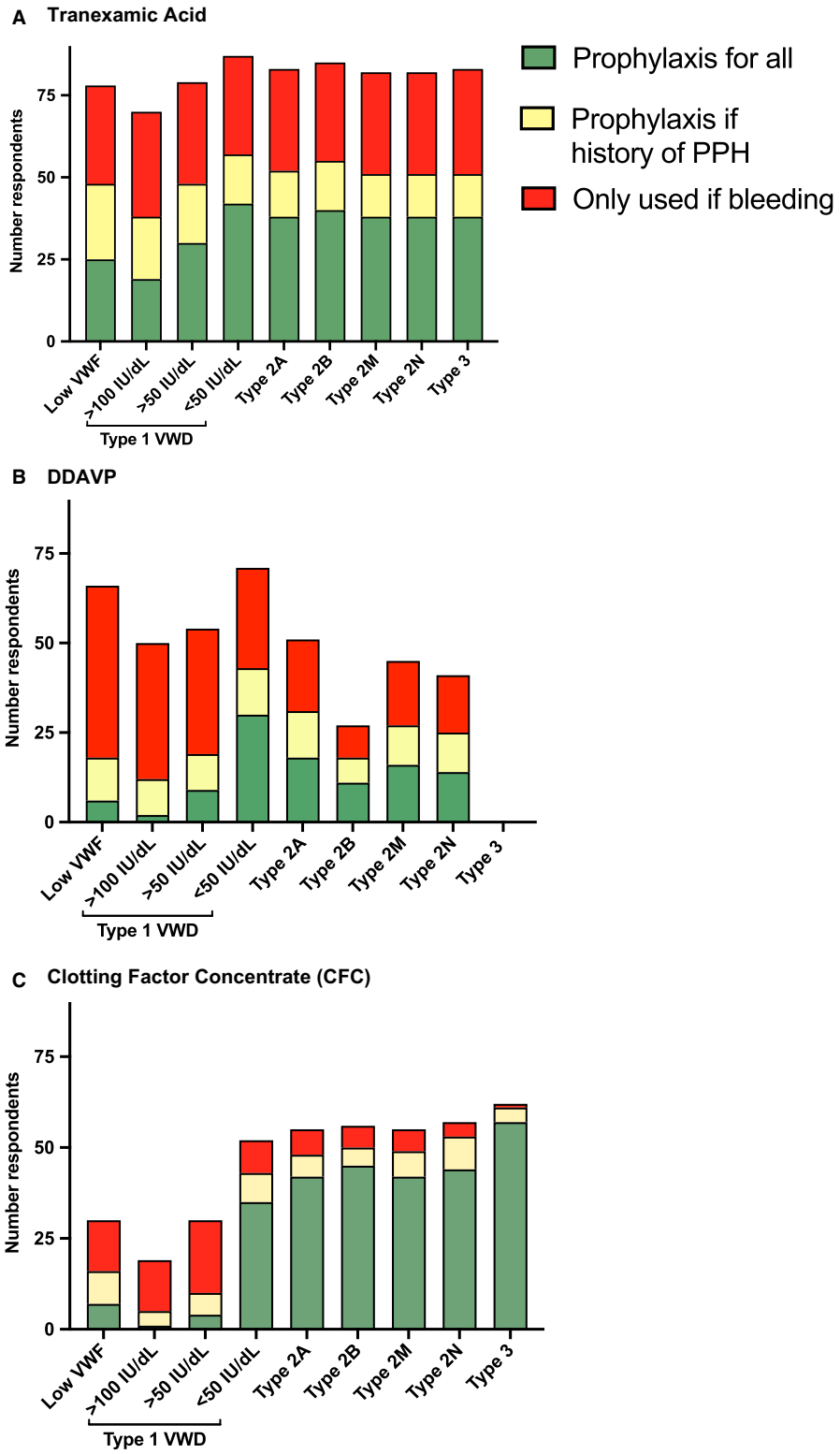

FIGURE 3 Hemostatic cover (tranexamic acid, A; desmopressin, DDAVP, B; VWF containing clotting factor concentrate [CFC], C) advised at delivery by VWD subtype and third trimester plasma VWF levels. PPH, postpartum hemorrhage; VWD, von Willebrand disease; VWF, von Willebrand factor

Women with VWD are also at a heightened risk of secondary PPH, excess bleeding occurring between >24 h and 6 weeks postpartum. Secondary PPH rates in women with VWD range from 5–32%, compared to 2% in the general postpartum population.[6] Secondary PPH may be heralded by prolonged (>6 weeks) or heavy lochia. Our survey (n = 79) indicated that duration or flow of lochia is not routinely collected (22.8%), with standardized capture via electronic patient records (EPRs) occurring in only 15.2% or else reliant on patient (33%) or obstetrician (29.1%) reporting. Depending on the location, postpartum follow-up may be with family doctors rather than obstetricians so using this approach will only identify those with early PPH or who re-present to the obstetric hospital for acute review. Given the elevated risk profile of women with VWD for secondary PPH, improved recognition and postpartum surveillance is directly needed.

TABLE 1 Frequency of suggested peripartum monitoring of plasma VWF levels by VWD subtype

Disease subtype (number of respondents)	Timing of blood sampling peripartum					
	Onset of labor, delivery & in 1st week postpartum	Onset of labor/delivery only	At delivery & in 1st week postpartum	Only in 1st week postpartum	At onset of labor & at delivery	Other
	Percentage respondents (%)					
Low VWF/Type1 VWD ($n = 68$)	16.2	26.5	28	11.8	5.9	11.6
Type 2 VWD ($n = 83$)	32.5	22.9	18.1	6	6	14.5
Type 3 VWD ($n = 93$)	43	20.4	11.8	6.5	4.3	14

Abbreviations: VWD, von Willebrand disease; VWF, von Willebrand factor.

4 | DISCUSSION

This is the first global survey focusing on the clinical management of women with VWD in pregnancy. With responses from 39 countries, in both English and Spanish, it provides a snapshot of clinical practices internationally and underscores the areas of clinical uncertainty. Survey data are always limited by the number of respondents; with the responses of 132 physicians managing women with VWD from a variety of clinical settings and practice sizes internationally we believe a representative sample has been provided. One limitation of note is that not all respondents answered every question; this may have reflected uncertainty regarding areas of clinical practice. In order to highlight this issue the number of respondents for each question are outlined. The care of these patients is almost always multidisciplinary and another limitation of our survey is that we did not survey for obstetrical interventions such as the use of multiple uterotonics.

Antenatal assessment of plasma VWF levels is critical in pregnant women with all subtypes of VWD as the pregnancy-induced physiological increase in plasma VWF levels may be blunted (low VWF, some women with type 1 VWD) or markedly reduced/absent (variable for women with type 1 VWD, poor responses often seen in type 2 VWD, no response in women with type 3 VWD). Failure to evaluate plasma VWF levels in pregnancy has been associated with higher rates of PPH at delivery.[25] As a result, both Royal (UK) and American Colleges of Obstetricians and Gynecologists (RCOG, ACOG) recommend the antenatal assessment of plasma VWF levels in women with VWD, although their guidance differs in frequency.[13,18] The RCOG advise assessment of plasma VWF levels at booking, third trimester, and prior to any invasive procedures, with the ACOG favoring third trimester assessment to facilitate delivery planning.[13,18] In our survey, nearly all respondents assess plasma VWF levels in the third trimester (94.7%) in preparation for delivery; however, testing in other trimesters remains inconsistent. For women with low VWF levels, 43.8% do not repeat levels once within the normal (non-pregnant) reference range. Use of non-pregnant reference ranges in this clinical context is fraught as plasma VWF levels in pregnant women with type 1 VWD remain consistently lower than their healthy pregnant peers and bleeding may still occur at delivery.[2,9]

The management of delivery identified multiple areas of differing practices. Divergent approaches to recommendations regarding the use of NA for women with VWD were clearly evident, with many European physicians advising against the use in contrast to North American respondents. There remain concerns that with CFC supplementation plasma, but not platelet VWF, will be corrected and a bleeding risk may persist. In the general obstetric population the rate of epidural hematoma is low (1/168,000);[26,27] however, the risk in women with VWD is hampered by the limited, small clinical studies. The recent VWD guidelines examine the optimal target plasma VWF:Act level in women proceeding to neuraxial anesthesia; however, they explicitly state that suitability for NA was not addressed, remarking that this decision involved an individualized, complex assessment outside the scope of the guidelines.[14] In the absence of definitive guidance, harmonization of practice internationally is likely to remain challenging.

An area of significant current controversy is the ideal target plasma VWF required at delivery to prevent excess bleeding. While most respondents target a trough plasma VWF level of 50 IU/dL, 19% of respondents use a higher trough of ≥100 IU/dL. These differing approaches are currently the focus of clinical trials that will provide insight into the optimal approach.[28,29] Recommendations regarding the optimal duration of replacement therapy also differed with approximately 60% treating for 3–5 days for SVD and 5–7 days for a LSCS, but both longer and shorter durations suggested by other respondents. Prophylactic TXA use for the peripartum management of women with VWD varied considerably, even within the same disease subtype (22% for women with type 1 VWD and plasma VWF levels>100 IU/dL, 49% for those type 1 VWD and levels <50 IU/dL). Since this survey, the 2021 VWD management guidelines have recently been published, suggesting the use of TXA in women with VWD during the postpartum period (for 10–14 days postpartum or longer if bleeding remains heavy). [14] This significant practice change was made on low certainty of the evidence of effects but placed a high value on the benefits of prevention and treatment of significant hemorrhage and the small harms of this intervention for pregnant women with VWD.[14]

Following delivery, plasma VWF and FVIII levels decline, returning to baseline by 3 weeks postpartum.[9] Respondents

reported similar approaches to laboratory monitoring postpartum with VWF:Act assays advised by 97.6%, most frequently in combination with both VWF:Ag and FVIII (71.1%). The limited availability of VWF:GpIb assays was evident, with their use reported by only 13% of participants.

Antenatal anemia has been associated with PPH[30–32] with antenatal hemoglobin <9 g/dL conferring a 2-fold increased risk of severe PPH requiring transfusion[31] and severe antenatal anemia (hemoglobin <7 g/dL) increasing the risk of PPH 10-fold.[32] Although studies have hypothesized that severe anemia may impair myometrial contractility due to reduced oxygenation, increasing the risk of uterine atony,[30] the precise mechanism(s) through which anemia heightens PPH risk are unclear. Recent ACOG guidance recommends screening for anemia in the first trimester and again at 24-28/40 weeks gestation as well as low-dose iron supplementation for all pregnant women.[33] Similarly, the RCOG recommends antepartum hemoglobin assessment (with iron supplementation if required) to reduce the morbidity associated with anemia and PPH.[23] In our survey, antenatal hemoglobin assessment was routinely performed (93% of respondents) but, despite the susceptibility of women with VWD to secondary PPH (reported rates in case series in excess of 30%[11,34,35]) only 67.4% of respondents check iron and/or hemoglobin in the postpartum period. Secondary PPH in the general obstetric population is usually as a result of infection and/or retained placenta.[36] As women with VWD may present with excess bleeding but without signs of infection/inflammation, their symptoms may be dismissed. An improved awareness among obstetricians, general physicians, and hematologists of their unique vulnerability in this period; improved postpartum monitoring; and extended use of tranexamic acid is directly required. Accompanying the new 2021 VWD guidelines[14] are the first agreed definitions for both primary (blood loss >1000 mL within 24 h of birth or any blood loss with the potential to produce hemodynamic instability) and secondary PPH (blood loss that is heavier than normal lochial loss between 24 h and 6 weeks postpartum and necessitates medical review or intervention or which lasts beyond 6 weeks after childbirth) in women with VWD, an important step forward in both clinical care and reseach.[37] Through providing a unified approach to the diagnosis of PPH it is hoped that both identification and management can be improved for pregnant women with VWD.[37,38]

Finally, despite advances in hemophilia therapeutics internationally, global product availability for the treatment of VWD remains a challenge. Despite a broadening choice of VWF replacement therapies with the introduction of rVWF, 4.7% of respondents still report access only to cryoprecipitate or fresh frozen plasma for peripartum prophylaxis.

5 | CONCLUSIONS

This work highlighted important issues regarding the management of women with VWD, one of the most common bleeding disorders worldwide. The recent American Society of Hematology (ASH)/ ISTH/ National Hemophilia Foundation (NHF)/World Federation of Hemophilia (WFH) VWD 2021 guidelines have addressed two important pregnancy-focused questions:the optimal target for NA and the role of postpartum prophylactic TXA. However, the results of our survey have highlighted the considerable disparities that exist in care for pregnant women with VWD and the ongoing uncertainty regarding suitability for NA as well as antenatal and postpartum monitoring.[14] These challenges experienced by physicians in the management of pregnant women with VWD relate to the scarcity of robust large-scale clinical research in this area. With new standardized definitions we can start to harmonize care and research internationally.[37] In harnessing the communal expertise afforded through the ISTH networks we have the opportunity to develop international collaborative projects to address both the knowledge gaps in the current guidelines and the clinical issues raised in this survey. While improving care for pregnant women with VWD, the importance of equitable access to appropriate treatment must not be forgotten, with VWF-specific replacement therapies still not available in some settings. With these challenges in mind, it is incumbent on our community to achieve these goals so that women with VWD internationally can be afforded the best possible multidisciplinary peripartum care.

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CONFLICTS OF INTEREST

M.L. has served on an advisory board for Tremeau Pharmaceuticals, received research and consultancy funding from Takeda, and acted as a consultant for Sobi. A.S.L. has received an Investigator Initiated Research grant from Takeda. P.K. is a consultant for Tremeau Pharmaceuticals and Uniqure. S.L.H and R.A.K. have no conflicts of interest. J.S.O'D. has served on speakers' bureaus for Baxter, Bayer, Novo Nordisk, Boehringer Ingelheim, Takeda, Leo Pharma, and Octapharma. He has also served on the advisory boards of Baxter, Bayer, Octapharma CSL Behring, Daiichi Sankyo, Takeda, Boehringer Ingelheim, and Pfizer. J.S.O'D. has also received research grant funding awards from Baxter, Bayer, Pfizer, Shire, Takeda, and Novo Nordisk. R.I.B. has served on the speaker's bureau for Bayer and also served on the scientific advisory boards of Roche and Janssen-Cileg. R.I.B.'s institution has received research grant/clinical trial funding from Bayer, Takeda, Pfizer, Daiichi Sankyo, CSL Behring, Roche, Amgen, Celgene, Rigel Pharmaceuticals, Abbvie, Sanofi, MorphoSys AG, Acerta Pharma, Jansen-Cileg, Bristol-Myers Squibb, Boehringer Ingelheim, Portola, Technoclone, and Alexion.

AUTHOR CONTRIBUTIONS

M.L., J.S.O'D., A.S.L. designed the survey; A.S.L. provided a Spanish translation; P.K., M.O., S.H. reviewed the survey; M.L. collected and analyzed the data. All authors (M.L., A.S.L, P.K., R.A.K., J.S.O'D. R.I.B., M.O., S.H.) were involved in writing and reviewing the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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