Contemporary issues in the management of von Willebrand disease

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Summary
Von Willebrand disease (VWD) is the most common inherited bleeding disorder. Bleeding scores in VWD, focused in particular on mucosal bleeding, can be very useful in the diagnosis and validation of different types of treatment. The results of an extended prospective study with a large amount of information on clinical phenotype and implications in treatment are reviewed in this article. Treatment of mucosal and joint bleeding in severe VWD remains difficult in some patients. Due to the lack of data on the use of prophylaxis in these patients it is difficult to establish optimal treatment regimens. An overview of the literature, with a focus on the ongoing PRO.WILL study, is provided here. Furthermore, understanding the changes in von Willebrand factor (VWF) levels during pregnancy is very important for establishing the optimal management strategy for pregnancy and delivery in women with VWD. A recently published prospective observational cohort study in women with and without VWD during the postpartum period provides important data that should allow the improvement of postpartum treatment protocols.

Keywords
von Willebrand disease, prophylaxis, pregnancy, bleeding score, FVIII/VWF concentrates

Bleeding score: implications for treatment

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Von Willebrand disease (VWD), the most common inherited bleeding disorder, occurs as a result of quantitative (VWD3 and VWD1) and/or qualitative (VWD2A, VWD2B, VWD2M, VWD2N) defects in von Willebrand factor (VWF). In severe VWD3, VWD1 and VWD2N, factor VIII (FVIII) is also reduced. Despite the complex and heterogeneous nature of VWF defects, all VWD types can currently be managed efficiently in most patients. However, although correct VWD diagnosis and classification is required in order to provide the optimal therapeutic approach, it is not always possible to achieve accurate diagnosis and classification. In contrast to haemophilia A which is classified easily as severe, moderate or mild depending on baseline FVIII levels, the severity of VWD is not presently well defined within VWD types.

With regard to the management of different VWD forms, our experience in Italy over more than a decade has taught us that clinical and laboratory VWD data obtained from registries and/or retrospective studies are not always reliable due to incorrect laboratory tests for VWD diagnosis and classification at some local sites (1). Therefore, only prospective studies on VWD with laboratory parameters evaluated by an expert centre should be considered in clinical trials (2).

Based on this background, we designed a prospective observational cohort study (RENAWI-2) which is the continuation of a previous retrospective Italian registry on VWD (RENAWI-1) (1). Full details of RENAWI-2 have been published previously (2); the current section provides a summary of the study. RENAWI-2 was carried out in adult VWD patients with a centrally confirmed diagnosis and followed-up at six Italian haemophilia centres (all members of the Italian Association of Hemophilia Centers, AICE). The objectives of RENAWI-2 were to evaluate the incidence, types and severity of spontaneous bleeding episodes requiring DDAVP (1-deamino-8-d-arginine vasopressin) and/or VWF/FVIII concentrates in a large cohort of adult VWD patients: i.e. how to characterise bleeding phenotype in different VWD types and to predict clinical outcome in these patients.

Criteria for correct diagnosis of VWD were bleeding history, low VWF activity and inheritance. Patients were included in RENAWI-2 if their VWF ristocetin cofactor (VWF:RCo) activity levels were below the lower normal limits of the central laboratory (56 IU/dL), corresponding to two standard deviations below the plasma levels of normal individuals with non-O blood group. VWD patients with liver diseases and cancer, as well as those undergoing prophylaxis at enrolment, were excluded (2). Bleeding score was calculated by the investigators based on symptoms that had occurred before inclusion in RENAWI-2 using a standardized questionnaire (3) which was administered to patients when blood samples were withdrawn at the beginning of the one-year prospective follow-up.
Figure 1 shows the patient flow, from the original RENAWI-1 cohort study into RENAWI-2. At least one spontaneous bleeding event requiring treatment during the one-year follow-up period in RENAWI-2 occurred in only 75 of the total 796 cases (9.4%), and these patients were defined as bleeders (VWD1: 23/457; VWD2A: 10/65; VWD2B: 5/56; VWD2M: 12/169; VWD3: 25/49). With regard to baseline VWF:RCo levels, 34%, 28% and 38% of cases were classified as mild (31–56 IU/dl), moderate (10–30 IU/dl) or severe (<10 IU/dl), respectively, with differences within the VWD types (2).

The age- and sex-adjusted relationship between VWF:RCo plasma levels and bleeding score in all RENAWI-2 patients with VWD showed a plateau at a mean bleeding score of 3.5 that was achieved for VWF:RCo levels >30 IU/dl. A Cox’s proportional hazards model was used to predict the risk of bleeding (mucosal and non-mucosal) in different categories (bleeding score: <5, 5–10, >10; VWF:RCo: <10, 10–30, 31–54 (IU/dl); FVIII:C: <20, 20–40, >40 (IU/dl)). Higher bleeding scores and lower VWF:RCo and FVIII:C values were associated with an increased rate of bleeding (Figure 2). Based on the 796 cases in RENAWI-2 (of the 1234 confirmed cases in RENAWI-1), crude (unadjusted) hazard ratios (HR) associated with a high risk of bleeding were: bleeding score >10 (HR 6.80; 95% confidence interval [CI] 3.80–12.30), VWF:RCo <10 IU/dl (HR 3.27; 95% CI 1.77–6.06) and FVIII:C <20 IU/dl (HR 14; 95% CI 2.43–7.26). By multivariate model, adjusted for all variables, a bleeding score >10 (HR 7.27; 95% CI 3.83–13.83) was the most significant determinant of bleeding risk (2).

According to Kaplan-Meier analysis of data from RENAWI-2, bleeding event-free survival at 12 months was lower in VWD1 patients with a bleeding score >10 and VWF:RCo <10 IU/dl (HR 0.81 [95% CI 0.62–0.99]) or in VWD3 patients with a bleeding score >10 and FVIII levels <5 IU/dl (0.39 [95% CI:0.16–0.62]). In patients with VWD2A, VWD2B, and VWD2M analysed both separately and together, there was a non-statistically significant difference in bleeding event-free survival according to bleeding score and VWF:RCo levels. In patients with VWD3 in RENAWI-2, event-free survival rates differed markedly according to bleeding score and FVIII (2); however, because the patient population with VWD3 in RENAWI-2 was relatively small (n=49), this prompted the design of an international prospective study (3WINTERS-IPS) in a larger population of patients with VWD3 who will be followed-up for two years (4). The 3WINTERS-IPS recruitment target of 250 VWD3 patients has been reached, with patients being enrolled using homogenous and standardised criteria (4). A previous cohort study of 67 patients with VWD2B demonstrated that predicting thrombocytopenia by measuring VWF in its platelet receptor glycoprotein Ib-alpha-binding conformation is important because a low platelet count is an independent risk factor for bleeding (5). Prospective evaluation of 60 heterozygous patients with VWD1 carrying the R1205H VWF mutation and 23

Figure 2: Bleeding incidence assessed by Cox’s proportional hazard model in RENAWI-2. Republished with permission from The American Society of Hematology “The bleeding score predicts clinical outcomes and replacement therapy in adults with von Willebrand disease.” Federici et al. Blood 2014; 123: 4037–4044; permission conveyed through Copyright Clearance Center, Inc.
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with the C1130F mutation, both characterised by markedly increased VWF clearance, showed that the rate of spontaneous bleeding requiring coagulation/treatment was 7.5/100 patients-year in patients with the C1130F mutation compared with 1.9/100 patients-year in those with the R1205H mutation (p=0.004) (6). The authors proposed that different multimer patterns (characterised by the presence of ultra-large, theoretically more haemostatically-efficient VWF multimers in the plasma of patients with the R1205H mutation compared with the relative reduction of high-molecular-weight multimers observed in patients with the C1130F mutation) may protect better from bleeding in patients with the R1205H mutation (6). Although a greater bleeding tendency was observed in patients with VWD2A than in patients with VWD2M in another prospective cohort study (n=107), the difference could not be explained by FVIII or VWF levels and appeared to be due mainly to an increased incidence of gastrointestinal bleeding in VWD2A patients (7).

Although the bleeding event-free survival rate was different in VWD types in RENAWI-2, only a bleeding score >10 could predict for each type which patient had bleeding events severe enough to require treatment with DDAVP and/or concentrates. With regard to the treatment of bleeding events in RENAWI-2, for both DDAVP (Figure 3A) and VWF/FVIII concentrates (Figure 3B), cumulative dosages progressively increased with increasing bleeding scores. Pertaining to VWF/FVIII concentrates, a few patients with severe forms of VWD1 were treated with median annual VWF/FVIII concentrate dosages similar to those used for VWD3 patients. As a result of the intensive on-demand treatment needed for recurrent spontaneous bleeds, 12 of 53 patients (23%) were switched by the investigators to long-term prophylaxis at the end of the 12-month follow-up period, because of their frequent and/or severe bleeding episodes. All 12 of these VWD patients had very high bleeding scores (median, 22; range, 11–33) (2).

In summary, RENAWI-2 demonstrated that the bleeding score helps to predict clinical outcomes in adult patients with VWD. Moreover, high bleeding scores correlate with intensive on-demand therapy and may identify cases requiring regular prophylaxis.

Benefits of prophylaxis in VWD

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The benefits of prophylaxis in patients with haemophilia have been well established for many years and include reduced bleeds, preservation of joint function, and reduced morbidity and mortality (8–10). However, prophylaxis in VWD is less common. Treatment options in patients with VWD include FVIII/VWD concentrates and DDAVP (11–13). Prophylactic treatment has been shown to be useful in certain patients, including those with severe VWD types with recurrent bleeds, although data are limited. Prophylaxis is recommended in some treatment guidelines (13) and is not used widely: for example, the VWD Prophylactic Network (VWD PN), initiated to study the natural history of VWD bleeding and to prospectively study the role of prophylactic FVIII/VWF concentrates in severe VWD, identified a total 5343 patients for enrolment between February and July 2005, 991 of whom were treated with plasma-derived products in the preceding 12 months, and only 99 patients received prophylaxis, predominantly due to joint-related bleeds (14).

Unfortunately, currently available information about prophylaxis in patients with VWD is limited and clear evidence is still lacking with regard to when prophylaxis should be initiated, which patients should receive prophylaxis, and which prophylactic regimen is recommended. To date, data are available from national registries, industry-sponsored trials, and from cohorts including the VWD PN and, more recently, from prospective studies.

Data from the Swedish cohort, based on 35 patients with VWD 3 (n=28), VWD2A or 2B (n=6), or VWD1 (n=1) who received prophylaxis, showed that indications and experience with

Figure 3: Bleeding score as a predictor of clinical outcomes. Treatment of bleeding events with DDAVP (A) or VWF/FVIII (B) concentrates according to bleeding score in different VWF types. Republished with permission from The American Society of Hematology "The bleeding score predicts clinical outcomes and replacement therapy in adults with von Willebrand disease." Federici et al. Blood 2014; 123: 4037–4044; permission conveyed through Copyright Clearance Center, Inc.

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Prophylaxis varied with age (15, 16). In patients aged <5 years, virtually all VWD patients who initiated prophylaxis had mucosal (nose/mouth) bleeds, whereas patients aged 5–15 years had mucosal or joint bleeds and patients aged >15 years mostly had joint or gastrointestinal/menstrual bleeds. Patients received FVIII/ VWF prophylaxis (dosed 12–50 IU/kg FVIII, mean 24 IU/kg) at least once a week. Overall, prophylactic treatment was associated with a marked reduction of bleeding episodes, from ‘frequent’ (before treatment) to post-treatment annual bleeding rates (ABRs) of 0.3 (joint bleeds) or 0.4 (mucosal bleeds) (15). Prophylaxis was also associated with a reduction in required blood transfusions, although two patients with type 2 VWD required transfusion for gastrointestinal bleeding, despite prophylaxis. Clinical signs of arthropathy were also documented and observed in these patients with severe VWD. Strikingly, no clinical signs of arthropathy were observed if prophylaxis was started when patients were aged <5 years (15).

A German cohort study, evaluating long-term secondary prophylaxis in patients with VWD, enrolled 82 patients with clinically-relevant bleeding episodes and 32 of these patients (VWD1: 4 patients, VWD2: 15, VWD3: 20) received secondary prophylactic VWF replacement therapy (17). The initiation of prophylaxis was based on a bleeding score >2 prior to diagnosis, concomitant with recurrent bleeds associated with anaemia in patients with on-demand VWD therapy (17). Prophylaxis was administered 2–4 times per week. After 12 months of prophylaxis, haemoglobin levels normalized and the monthly bleeding frequency and bleeding score were reduced significantly compared with pre-prophylaxis/prediagnostic values (3 vs. 0.07; 3 vs. 0: p<0.001). Recurrent bleeding episodes stopped in 31 of 32 patients, although an inhibitor developed in one patient (17).

Reports from the international VWD PN study included 59 children and adults with VWD (median age at onset of prophylaxis: 22.4 years; VWD1: five patients, VWD2: 20 patients, VWD3: 34 patients). Observed bleeds were mainly mucosal, although joint bleeds increased with lower FVIII levels (18). ABRs observed within individuals on prophylaxis were significantly reduced compared to pre-study treatment for the total patient group (p<0.0001), and for those with primary bleeding indications of epistaxis (p=0.0005), joint bleeding (p=0.002) and gastrointestinal bleeding (p=0.001). Thus, the authors concluded that the prophylactic treatment of VWD is efficacious (18).

Data from a VWD PN prospective study, in which the effect of escalating-dose prophylaxis was evaluated in patients with severe VWD, were published recently (19). Patients were eligible for inclusion if they had VWD1 with VWF:RCo activity levels ≤20 % and/or FVIII ≤20 % and were unresponsive to desmopressin, had VWD2 and were unresponsive to desmopressin, or had VWD2B or VWD3. Out of 13 patients enrolled, 11 completed the study (VWD2A: six patients, VWD3: five patients). At enrolment, patients had epistaxis (n=6), gastrointestinal bleeding (n=3), or joint bleeding (n=2). Subjects entering the study began treatment at dosage level 1 (50 IU VWF:RCo/kg once weekly) and remained on this dose until meeting the criteria for escalation to level 2 (50 IU VWF:RCo/kg/twice weekly), or level 3 (50 IU VWF:RCo/kg/three times weekly) (19). Criteria for dose escalation levels are discussed in detail in the original publication by Abshire et al. (19) but, overall, involved one significant breakthrough bleeding episode despite compliant prophylaxis. The majority of patients with epistaxis remained in level 1, those with joint bleeds often needed to be escalated to level 2 or 3, and those with gastrointestinal bleeds were escalated to level 2, 3 or beyond. Prophylaxis decreased the median
ABR from 25 (prior to prophylaxis) to 6.1, and this reduced even further (4.0) when subjects reached their final dosing level (19).

A recent analysis of largely retrospective data from the VWD PN study evaluated bleeding patterns in 105 VWD patients (10 patients were treated prospectively) after long-term prophylactic replacement therapy (20). Inclusion criteria allowed patients with all VWD types and that were defined as non-responsive to DDAVP. Patients had to have a documented and defined bleeding history. The main types of bleeding event were epistaxis (32.7% of patients), gastrointestinal (23.2%) and joint (23.0%). Figure 4 shows the changes in bleeding pattern: compared with before treatment, there was an overall reduction in bleeding frequency following prophylaxis which differed according to VWD type and by the types of bleeding. The median reductions in ABRs were significant for epistaxis (p<0.0001), gastrointestinal bleeding (p=0.0003), joint bleeding (p<0.0001) and menorrhagia (p=0.008) (20).

Data from these various studies indicate that prophylaxis is superior to on-demand treatment and also raise the question of whether prophylaxis is effective enough. A crude and simplistic comparison of data from two separate studies, which evaluated prophylaxis in patients with haemophilia A (21) or VWD (19), shows that there are generally comparable reductions in ABR between the two patient groups (93% vs. 84%). Therefore, in the relatively small number of patients with severe VWD that have been evaluated to date, prophylaxis is effective in reducing bleeding rates, but further data are needed.

The evidence base for prophylaxis in severe VWD will be further strengthened by ongoing prospective studies such as the PRO.WILL study, a multicentre, open-label, randomised trial, which started in 2008 in Europe (22). The primary objective of the PRO.WILL study is to evaluate whether secondary prophylaxis with highly-purified plasma-derived FVIII/VWF concentrates (Fanhdi and Alphanate®), compared with the same treatment on-demand, prevents spontaneous bleeding in patients (aged >6 years) with severe VWD who are unresponsive to DDAVP (or in whom DDAVP is contraindicated) and experience frequent bleeding events. One of the main features of the PRO.WILL study design (Figure 5) is randomisation of patients to prophylaxis (VWF:RCo 60 IU kg⁻¹ every 2 or 3 days, depending on the type of bleeding event) or on-demand treatment (according to standard recommendations) and a follow-up period of 12 months. Interim results from PRO.WILL reported data from 12 patients (prophylaxis: 5 patients, on-demand: 7 patients) treated for >6 months (23). Median age at study inclusion was 55.1 (range 18–78) years. Bleeding episodes were observed in 100% and 60% of on-demand and prophylaxis patients, respectively. The total number of bleeding episodes was 58 and 20 in the on-demand and prophylaxis groups, respectively. Of these events, 53 (91%) and nine (45%) in the on-demand and prophylaxis groups, respectively, required treatment with FVIII/VWF concentrate. There was a reduction in epistaxis, haemarthrosis and muscular haematoma but not in gastrointestinal bleeds; however, at interim analysis, gastrointestinal bleeds were overrepresented in the prophylaxis group and this requires further investigation in the final analysis. No study drug-related adverse events or thrombotic events occurred. PRO.WILL has closed for enrolment with a total of 19 patients randomised, and final results are anticipated in late 2016. Based on the interim analysis, although further evaluation of prophylaxis in gastrointestinal bleeds is required, secondary prophylaxis with highly-purified FVIII/VWF concentrate is beneficial in severe VWD.

Decisions regarding which VWD patients should receive prophylaxis depend on the severity of VWD, bleeding history (treatment, need for blood transfusion, quality of life), treatment history (response to DDAVP), associated morbidity, and individual needs. It is important to note that bleeding score predicts outcome and may help to identify patients for a prophylactic treatment regimen (2).

In summary, studies conducted to date show that prophylaxis in VWD is effective. However, further trials are needed to define optimal dosing and indications. Final data from the ongoing PRO.WILL study will add to current knowledge on prophylaxis in VWD. In order to provide greater benefit to patients, prophylaxis needs to be implemented further into clinical routine based on data from clinical trials and registries.
Pregnancy and post-partum management of patients with VWD

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In addition to menstrual bleeding, women with VWD are particularly vulnerable to postpartum haemorrhage and the need for transfusion at the time of delivery (24–28). At the time of delivery, women with VWD may benefit from prophylaxis with VWF concentrates, with current recommendations suggesting treatment for 3–5 days (29). However, the optimal duration and frequency of postpartum prophylaxis at delivery are currently unknown. Although it has been shown that VWF and FVIII levels increase progressively through pregnancy (30–32), the timing of the return to baseline levels is not known, and even less is known about the levels in women with VWD, where information is limited to case reports (33). Consequently, there are currently insufficient data to guide clinicians (34).

This section provides an overview of a recently published prospective, observational cohort study conducted at six centres in the US, which was designed to elucidate the fall in VWF and FVIII activity after childbirth in women with and without VWD and in treated/untreated VWD patients at frequent intervals postpartum (35). The study was designed to estimate blood loss, not only at the time of delivery, but for six weeks postpartum, to allow us to infer the appropriate duration of postpartum treatment for women with VWD. The study population consisted of women aged ≥18 years in the 3rd trimester of pregnancy, with/without VWD. The sample size was based on the estimation that 20 women without VWD would be required to establish data curves. Individuals were excluded if they had a bleeding disorder other than VWD or were currently receiving anticoagulant medication. Subjects were included if the VWD diagnosis was confirmed by a haematologist. All typing and subtyping of VWD was performed at the individual study centres. For each individual with VWD, at least one individual without VWD was selected who matched the VWD individual by race and age (within 5 years), whenever possible. Prevention and management of bleeding episodes were at the discretion of the provider, but providers were asked to refrain from treating women with 3rd trimester VWF levels >50 IU/dl.

A complete blood count (CBC) and FVIII, VWF:RCo and VWF antigen (VWF:Ag) levels were obtained at approximately 36 weeks’ gestation, on admission for childbirth, and at 4 hour (h), 12 h, 1 day, 2 days, 3 days, 7 days, 14 days, 21 days, 28 days and 42 days postpartum. Study participants recorded postpartum blood loss using a modified pictorial blood assessment chart (PBAC; estimated blood loss: 1.0–5.5 ml, score 1; 5.6–15.5 ml, score 5; ≥15.6 ml, score 20). Details of prophylaxis were recorded in addition to pregnancy and delivery details, including mode of delivery, estimated blood loss (EBL) at the time of delivery (per the provider) and blood product usage.

Women with (n=32 [35 pregnancies]) and without (n=40 [40 pregnancies]) VWD were well-matched (no statistically significant between-group differences) with regard to age, ethnicity/race, parity and mode of delivery. The overall caesarean delivery rate in the study was 32.4%. In women without VWD, mean VWF levels in the 3rd trimester of pregnancy were 60–100% higher than baseline levels. Mean VWF levels peaked 12 h postpartum at 140–160% above baseline levels (i.e. approximately 250% of baseline values), and were significantly higher than the levels in the 3rd trimester or at any time after 24 h postpartum (p<0.05). The pattern of change for FVIII levels was in contrast to that for VWF. In the 3rd trimester, the mean FVIII level was 40–50% higher than baseline. Instead of rising immediately postpartum, FVIII levels began to fall. By 24 h postpartum, the mean FVIII level had dropped 20% before rising 30% to a mean peak value on postpartum day 3. This effect is likely explained by the normal thrombosis of pelvic veins that is observed in two-thirds of women at the time of delivery. FVIII levels then gradually declined to baseline by three weeks postpartum.

Figure 6: VWF:RCo, VWF:Ag and FVIII levels among treated subjects (circle) compared to levels among women with untreated type 1 VWD (square) and levels among women without VWD (triangle). Republished with permission from Blackwell Publishing “Postpartum von Willebrand factor levels in women with and without von Willebrand disease and implications for prophylaxis.” James et al. Haemophilia 2015; 21: 81–87; permission conveyed through Copyright Clearance Center, Inc.
Twenty-four of the 32 women with VWD had type 1 VWD. Of these, 17 women (70%) were deemed not to require treatment at the time of delivery (i.e. VWF levels had increased during pregnancy and were >50 IU/dl). Although their levels for each parameter were significantly lower, these untreated women had the same overall pattern of VWF:RCo, VWF:Ag, and FVIII levels as a matched subgroup of women without VWD. The mean EBL and haematocrits were not significantly different from those in women without VWD, with blood loss declining exponentially with each successive week (similar to that observed in women without VWD).

Fifteen women were treated during 17 pregnancies: type 1 VWD (7 women [46.7%]), type 2A (1 [6.7%]), type 2B (3 [20.0%]), type 2M (2 [13.3%]), type 2 of undefined subtype (1 [6.7%]), unknown VWD type (1 [6.7%]). Except immediately after delivery, VWF:RCo, VWF:Ag and FVIII levels among treated individuals appeared to parallel those among women without VWD. Although untreated VWD women had the same overall pattern of VWF:RCo, VWF:Ag, and FVIII levels as a matched subgroup of women without VWD, with blood loss declining exponentially with each successive week (similar to that observed in women without VWD).

The study authors acknowledged several limitations, including the fact that only one VWF concentrate was used (Humate-P®; CSL Behring, USA), most likely because two other VWF products were only recently approved for use in the US. In addition, no consistent protocol was followed and, consequently, treatment varied in intensity and duration, and data were not gathered on why a particular regimen was selected. Therefore, the impact of any particular protocol could not be evaluated. It was also recognised that larger studies are necessary in order to evaluate the impact of other variables, such as breastfeeding or mode of delivery, on VWF and FVIII levels and on blood loss. In contrast, the strengths of the study included the fact that frequent, serial sampling of VWF and FVIII was conducted and that there were sufficient subjects to achieve a sample size of approximately 20 observations for each assay at each time point. Furthermore, the study was able to provide some limited data on how women were treated for VWD postpartum, and provides justification for not treating women whose 3rd trimester VWF levels are >50 IU/dl. Indeed, the study provides reassurance for anaesthesiologists, that women whose VWF levels are >50 IU/dl in the 3rd trimester will have VWF levels >50 IU/dl intrapartum.

In summary, our study showed that VWF levels fall rapidly after delivery. Except in the immediate postpartum period, current treatment strategies do not raise VWF and FVIII levels to the levels of normal women or even to the levels of women with milder, untreated VWD. Although no postpartum haemorrhage manifested in our study, women with VWF levels ≤50 IU/dl at the time of delivery remain at risk for postpartum haemorrhage, despite treatment. Future studies might examine the impact of a more consistent and intensive postpartum protocol of at least 2–3 weeks duration.

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