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ORIGINAL ARTICLE *von Willebrand disease*

Postpartum von Willebrand factor levels in women with and without von Willebrand disease and implications for prophylaxis

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Summary. The aim of this study was to elucidate the fall in von Willebrand factor (VWF) and factor VIII activity (FVIII) after childbirth in women with and without von Willebrand disease (VWD). VWF:RCo, VWF:Ag, and FVIII were obtained in the third trimester of pregnancy, on admission for childbirth, and 10 times postpartum. Specimens were processed within 4 h and analysed centrally. Means were calculated at each time point. Forty women (40 pregnancies) without VWD and 32 women (35 pregnancies) with VWD were enrolled. 15/32 with VWD were treated (30% of those with type 1 and all of those with type 2) in 17 pregnancies. Treatments prior to delivery consisted of desmopressin (2/17), VWF concentrate (15/17) and after delivery VWF concentrate (16/17). Duration of treatment was 0–21 days (median 6). VWF levels peaked at 250% of baseline – 4 h postpartum in women with VWD and 12 h postpartum in women without VWD. Thereafter, VWF levels fell rapidly, approached baseline at 1 week and reached baseline at 3 weeks. Except immediately postpartum, when the levels among treated cases were higher, levels among women with VWD appeared to parallel, but were lower than those among women without VWD. Levels were lowest among those who received treatment. VWF levels fall rapidly after childbirth. Except immediately postpartum, current treatment strategies do not raise VWF levels to the levels of women without VWD or even to the levels of women with milder, untreated VWD. Consequently, women with VWD may be at risk of postpartum haemorrhage despite treatment.

Keywords: factor VIII, postpartum haemorrhage, pregnancy, von Willebrand disease, von Willebrand factor

Introduction

Retrospective studies show that women with von Willebrand disease (VWD) have a higher rate of postpartum haemorrhage and a higher rate of transfusion at the time of delivery compared to pregnant women without VWD. [1–5] Normally, postpartum haemorrhage is seemingly mitigated by a progressive increase through pregnancy and the third trimester of von Willebrand factor (VWF) and factor VIII activity (FVIII) levels, which peak at the time of delivery [6,7] and begin to fall thereafter [8]. These levels have been reported to decline to baseline within 1 month postpartum [9], but the laboratory pattern of these levels has not been comprehensively studied during the postpartum period. In only one study have interim levels been obtained. In that study, a level was obtained on each subject 1 – 3 weeks after delivery and these levels approached baseline [6]. Even less is known about the VWF and FVIII levels in women with VWD in whom information is limited to case reports [10]. Since women with VWD have not been studied intensively and longitudinally

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during the postpartum period, the presumption is that their VWF levels return to pre-pregnancy levels at least as quickly as they do in normal women, but there are insufficient data to guide clinicians.

The objectives for this study were: (i) to obtain VWF and FVIII levels in women with and without VWD and in treated and untreated patients at frequent intervals postpartum, (ii) to construct curves from these data, (iii) to estimate blood loss, not only at the time of delivery, but for 6 weeks postpartum and (iv) to make inferences about the appropriate duration of postpartum treatment for women with VWD based on these data.

Materials and methods

Study design

This was a prospective observational cohort study of women with VWD and without VWD during the postpartum period. Subjects were enrolled in the third trimester of pregnancy.

Setting

Subjects were enrolled from obstetric clinics and physician practices affiliated with five university medical centres and one community hospital in the United States (US) (Duke University Medical Center, Durham, NC; Hospital of the University of Pennsylvania, Philadelphia, PA; Mary M. Gooley Hemophilia Center at the Rochester General Hospital, Rochester, NY; Hemophilia Center of Western Pennsylvania, University of Pittsburgh, Pittsburgh, PA; Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ; and the Indiana Hemophilia & Thrombosis Center, Indianapolis, IN, USA). Subjects without VWD were enrolled from three of the sites (Duke University Medical Center, Mary M. Gooley Hemophilia Center at the Rochester General Hospital and Rutgers Robert Wood Johnson Medical School). Subjects were enrolled between January 1, 2007 and December 31, 2012.

Participants

The study population comprised pregnant women with and without VWD 18 years of age and older. Women with a bleeding disorder other than VWD or who were currently taking anticoagulant medication were excluded. The sample size was determined based on the estimation that 20 women without VWD would be required to establish curves. Women with VWD were included if the diagnosis was confirmed by a haematologist. All typing and subtyping of VWD were performed at the individual centres. Since VWF levels differ by race, an attempt was made to balance the groups by race and age using matching. For each subject with VWD, at least one subject without VWD was selected who matched the subject with VWD by race and age (within 5 years) whenever possible.

Study procedures

A complete blood count (CBC), FVIII, von Willebrand ristocetin cofactor activity (VWF:RCo) and von Willebrand factor antigen (VWF:Ag) were obtained at 12 different time points: in the third trimester at approximately 36 weeks' gestation, on admission for childbirth, and at 4 h, 12 h, 1 day, 2 days, 3 days, 7 days, 14 days, 21 days, 28 days, and 42 days postpartum. CBCs were performed locally. Specimens were processed within 4 h of venipuncture, stored at −80°C and then shipped to the Duke Clinical Coagulation Laboratory where they were run on a Dade Behring BCS Coagulation Analyser. Providers were not restricted to any particular product or form of treatment, but were asked, although not required, to refrain from prescribing prophylaxis with any haemostatic agent for women whose third trimester VWF levels were > 50 IU dL^{-1}. Details of prophylaxis were recorded as were details of the pregnancy and delivery such as mode of delivery, estimated blood loss (EBL) at the time of delivery (per the provider) and blood product usage.

Lochial blood loss was estimated by the subjects and summarized by the study staff. Subjects were each provided with the same brand and type of sanitary pads (Kotex® Maxi Pads, Kimberly-Clark, Dallas, TX, USA) and were asked to record their postpartum blood loss on a modified pictorial blood assessment chart. Lochial blood loss was estimated by the chart and by changes in haematocrit or haemoglobin. The chart used three different pictograms depicting three different degrees of saturation – minimal (slight), moderate and maximal (severe). The chart was corroborated by a panel of three observers (AHJ, BT and SKF). Consistent with methodology used to estimate degree of saturation of pads in previous studies [11,12], whole expired packed red blood cells were diluted to a uniform 57% haematocrit using 5% bovine serum albumin. Measured amounts of the diluted blood were applied to the centre of standardized pads until the three-person panel agreed that the pads correlated with the three different pictograms. Minimal saturation correlated with 0.1 mL to 5.5 mL and was assigned a score of 1. Moderate saturation correlated with 5.6–15.5 mL and was assigned a score of 5. Maximal saturation correlated with 16.5–33.5 mL and was assigned a score of 20.

Statistical analyses

Means were compared using ANOVA and Student's *t*-test. Statistical analyses were performed using JMP statistical software (SAS, Cary, NC, US).

Table 1. Characteristics of pregnancies in women with and without von Willebrand disease (VWD).

	With VWD (n = 35)	Without VWD (n = 40)	Significance
Mean age	28.8	30.6	NS
Race/ethnicity			
White	28 (80%)	29 (73%)	NS
African American	6 (17%)	7 (17%)	
Hispanic	1 (3%)	1 (3%)	
Asian	0	3 (7%)	
Parity			
Nulliparous	15 (43%)	9 (23%)	NS
Multiparous	16 (46%)	29 (72%)	
Unknown	4 (11%)	2 (5%)	
Mode of delivery			
Vaginal	21 (60%)	29 (72%)	NS
Caesarean	13 (37%)	11 (28%)	
Unknown	1 (3%)	0	

Results

Subjects

Forty women without VWD with 40 unique pregnancies were enrolled. Thirty-two women with VWD who had 35 pregnancies were enrolled and available for analyses. The age, race/ethnicity, parity and mode of delivery for the pregnancies in women with and without VWD are presented in Table 1. There was no difference between the mean age of the women with VWD (28.8 years) vs. women without VWD (30.6 years). The racial and ethnic distributions were nearly identical to that of the US population with 80% of the women with VWD and 73% of the women without VWD being white. Although there was a greater proportion of nulliparous women (43%) in the VWD group compared to the group without VWD (23%), the proportion was not statistically different. The overall caesarean delivery rate in the study was 32.4% compared to 32.8% for the US in 2012.

Women without VWD

VWF:RCo, VWF:Ag and FVIII measurements from the 40 women without VWD were used to establish means at various intervals postpartum and to construct curves. Among the 40 women without VWD, VWF:RCo and VWF:Ag levels fell rapidly after delivery, approached the nadir within 1 week and reached the nadir at 3 weeks postpartum. At 3 weeks postpartum, the levels plateaued and remained constant over the next 3 weeks. Levels at 6 weeks postpartum were presumed to be at baseline (see Fig. 1a and b). In the third trimester of pregnancy, mean VWF levels (VWF:RCo = 129 IU dL^{-1} [111, 146]; VWF:Ag = 186 IU dL^{-1} [160, 212]) were 60–100% higher than the baseline levels (VWF:RCo = 77 IU dL^{-1} [62, 92]; VWF:Ag = 96 IU dL^{-1} [84, 109]). Mean VWF levels peaked at 12 h postpartum [VWF:RCo = 199 IU dL^{-1} (162, 235); VWF:Ag = 236 IU dL^{-1} (208, 265)]. These levels were 140–160% above baseline (i.e. were approximately 250% of the baseline values), and were significantly higher than the levels in the third trimester of pregnancy 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 third trimester, the mean FVIII level [FVIII = 123 IU dL^{-1} (110, 135)] was 40–50% higher than baseline [FVIII = 83 IU dL^{-1} (74, 91)] ($P < 0.05$). Instead of rising in the immediate postpartum period, FVIII levels began to fall. By 24 h postpartum, the mean FVIII level had dropped 20% [FVIII = 103 IU dL^{-1} (93, 113)] before rising 30% to a mean peak value of 135 IU dL^{-1} (102, 167) on postpartum day 3 ($P < 0.05$). FVIII levels then gradually declined to baseline by 3 weeks postpartum [FVIII = 82 IU dL^{-1} (74, 91)] (see Fig. 1c).

None of the women without VWD had excessive bleeding during childbirth or postpartum, nor did they require any blood products. The mean EBL at delivery was 437 mL (346, 529). The mean haematocrit reached a nadir on postpartum day 1 at 31.3% (29.9, 32.8) down 10% from a value of 34.1% (33.1, 35.2) in the third trimester. The mean haematocrit was 38.7% (37.6, 39.7) at 6 weeks postpartum. The lochial blood loss declined exponentially with each successive week (see Fig. 2).

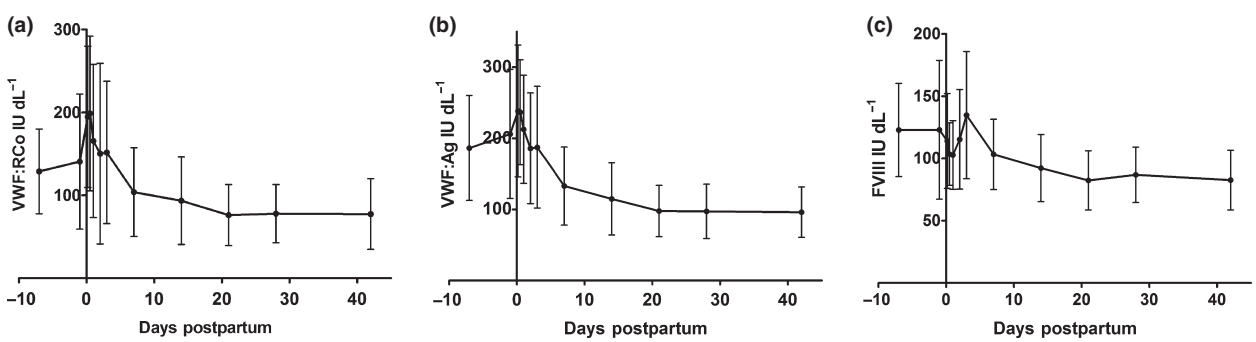

Fig. 1. VWF:RCo, VWF:Ag and FVIII levels among women without VWD.

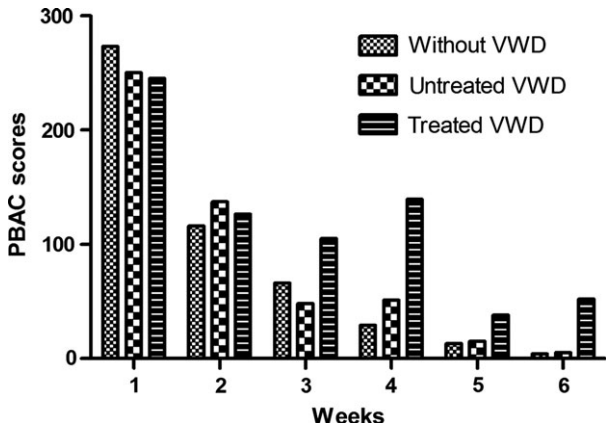

Fig. 2. Pictorial blood assessment chart scores by week postpartum.

Untreated women with type 1 VWD

Twenty-four of the 32 women with VWD had type 1. Of the eight women with VWD other than type 1, one had type 2A; three had type 2B; two had type 2M; one had type 2 of undefined subtype and one had an unknown type of VWD. All of these eight women plus seven of the women with type 1 VWD received treatment during 17 pregnancies and are presented later. Seventeen women comprising 70% of the type 1 VWD study subjects did not receive treatment, including treatment with any blood products during 18 pregnancies. VWF:RCo, VWF:Ag and FVIII levels were compared among these women and a subset of the women without VWD who were matched for age, parity and race/ethnicity. VWF:RCo, VWF:Ag and FVIII levels appeared to parallel those among women without VWD, but were significantly lower at almost every time point ($P < 0.05$). Figure 3 a–c. In the third trimester of pregnancy, mean VWF levels among women with untreated type 1 VWD [VWF:RCo = 73 IU dL^{-1} (95% CI 48, 99); VWF:Ag = 92 IU dL^{-1} (70, 115)] were 50–60% higher than the baseline levels at 6 weeks postpartum [VWF:RCo = 49 IU dL^{-1} (35, 64); VWF:Ag = 57 IU dL^{-1} (45, 69)]. On admission for childbirth, mean VWF levels were another 40–50% higher than the third trimester values [VWF:RCo = 102 IU dL^{-1} (73,132); VWF:Ag = 139 IU dL^{-1} (112, 166)]. In women without VWD, mean VWF levels peaked at 12 h postpartum, but in women with untreated type 1 VWD, mean VWF levels peaked at 4 h postpartum [VWF:RCo = 121 IU dL^{-1} (88, 154); VWF:Ag = 143 IU dL^{-1} (111, 176)]. As in women without VWD, these peak levels were 150% higher than the baseline (i.e. were approximately 250% of the baseline values).

Among untreated women with type 1 VWD, the pattern of change in FVIII levels was in contrast to the pattern of VWF levels. However, the 20% drop in FVIII observed immediately postpartum in women without VWD was not observed in women with VWD. In the third trimester, the mean FVIII level [FVIII = 92 IU dL^{-1} (77, 105)] was 30–40% higher than baseline [FVIII = 68 IU dL^{-1} (59, 78)] ($P < 0.05$). On admission for childbirth, in contrast to women without VWD, the mean FVIII level [FVIII = 106 IU dL^{-1} (91, 122)] was slightly higher (by 15%) than the third trimester value. Instead of rising in the immediate postpartum period, FVIII levels dropped, but not to the extent that levels dropped in women without VWD and by 12 h postpartum, only to a level observed in the third trimester. FVIII began to rise again and reached a peak mean value of 109 IU dL^{-1} (87, 132) on postpartum day three ($P < 0.05$). FVIII levels then gradually declined to baseline by 3 weeks postpartum where they remained constant.

None of these women had excessive bleeding during childbirth or postpartum, nor did they require any blood products. The mean EBL at delivery was 475 mL (332, 618). The mean haematocrit reached a nadir on postpartum day 1 at 31.6% (30.0, 33.2) down from 33.6% (32.0, 35.3) in the third trimester. The mean haematocrit was 38.6% (37.1, 40.1) at 6 weeks postpartum. The EBL and mean haematocrits were not significantly different from those in women without VWD. The lochial blood loss declined exponentially with each successive week as it did for women without VWD (see Fig. 2).

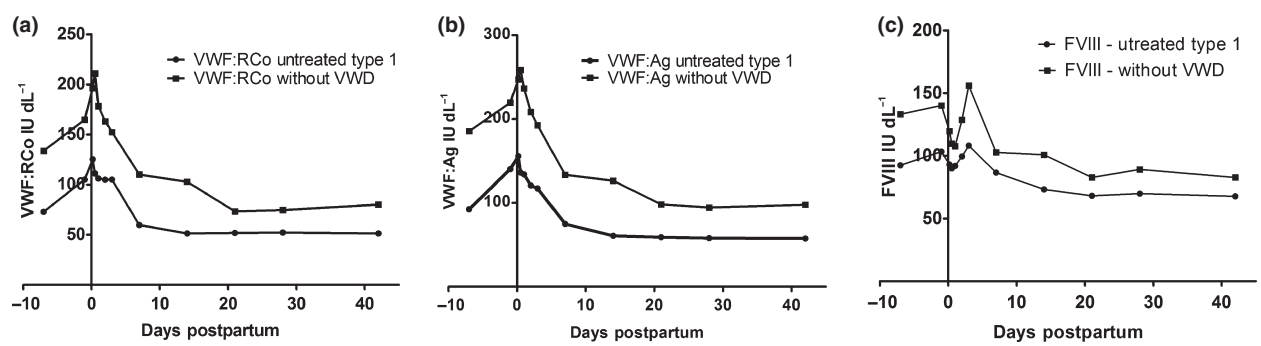

Fig. 3. VWF:RCo, VWF:Ag and FVIII levels among women with untreated type 1 VWD compared to those among women without VWD.

Treated women with VWD

Fifteen women were treated during 17 pregnancies – seven women with type 1 VWD; one with type 2A, three with type 2B, two with type 2M and one with type 2 of undefined subtype; and one with unknown type of VWD. Mean third trimester VWF and FVIII levels for this group were VWF:RCo = 34 IU dL^{-1} [95% CI 0, 75]; VWF:Ag = 63 IU dL^{-1} [31, 95]; FVIII = 65 IU dL^{-1} [44, 86]. Treatment prior to delivery consisted of VWF concentrate in 15/17 pregnancies and desmopressin in 2/17. None of the women received tranexamic acid or aminocaproic acid. VWF concentrate was administered postpartum after 16/17 deliveries. Duration of postpartum treatment ranged from 0 to 21 days (median length of treatment = 6 days). See Table 2 for treatment details. With one possible exception, treatment was prescribed for prophylaxis, not for treatment of bleeding. None of the subjects required any other blood products. Except immediately after delivery, VWF:RCo, VWF:Ag and FVIII levels among treated subjects appeared to parallel those among women without VWD or untreated subjects with type 1 VWD, but the levels remained lower. Overall, levels were lowest among the treated subjects (Fig. 4 a–c).

Among the treated women with VWD, only one was described as having 'excessive bleeding' during childbirth. She was subject 12 in Table 2 with type 2B VWD who received 21 days of postpartum treatment. Her EBL at delivery was 400 mL, which is actually a normal blood loss. The mean EBL at delivery for treated women, however, was 615 mL (473, 758), which was significantly greater than the mean for other women whose mean EBL was 448 mL (379, 517) ($P < 0.05$). The mean third trimester haematocrit for treated women was 34.5% (33.0, 36.0), the same as for other women. Although the mean haematocrit reached a nadir on postpartum day 1, similar to other women, the nadir haematocrit was 28.6% (26.7, 30.5), which was 20% lower than the third trimester value, and twice as low as the nadir for the other women ($P < 0.05$). There was no difference in the nadir between treated women with type 1 or type 2 VWD. The mean haematocrit for the treated women was 38.0% (36.4, 39.5) at 6 weeks postpartum, not significantly different from that of the other women. None of the treated women required any blood products other than VWF concentrate during the study. The lochial blood loss was equivalent to that of the other women

Table 2. Treatment of von Willebrand disease (VWD).

	Type of VWD	Treatment for delivery	Postpartum treatment	Total days postpartum (PP) prophylaxis
1a	1	VWF – continuous	VWF – continuous × 3 days; bolus × another 11 days	14
1b*	1	VWF – continuous	VWF – continuous × 3 days; bolus × another 11 days	14
2	2A	VWF – continuous	VWF – bolus × 2 weeks	14
3a	2M	VWF – bolus	VWF – bolus × 3 days	3
3b*	2M	VWF – bolus	VWF – bolus × 3 days	3
4	2B	VWF – bolus	VWF – bolus × 1 week	7
5	1	Desmopressin	VWF – bolus × 24 h	1
6	2B	VWF – bolus	VWF – bolus × 48 h	2
7	1	VWF – bolus	VWF – bolus × 21	21
8	1	VWF – continuous	VWF – continuous × 24 h; bolus × 1 dose 1 week PP	7
9	1	Desmopressin	VWF – bolus × 48 h	2
10	2(? subtype)	VWF – continuous	VWF – continuous × 6 days	6
11	2M	VWF – bolus	None	0
12	2B	VWF – bolus	VWF – bolus × 21 days	21
13	?	VWF – bolus	VWF – bolus × 8 days	8
14	1	VWF – bolus	VWF – bolus × 4 days	4
15	1	VWF – bolus	VWF – bolus × 48 h	2

*Subsequent pregnancy in same subject.

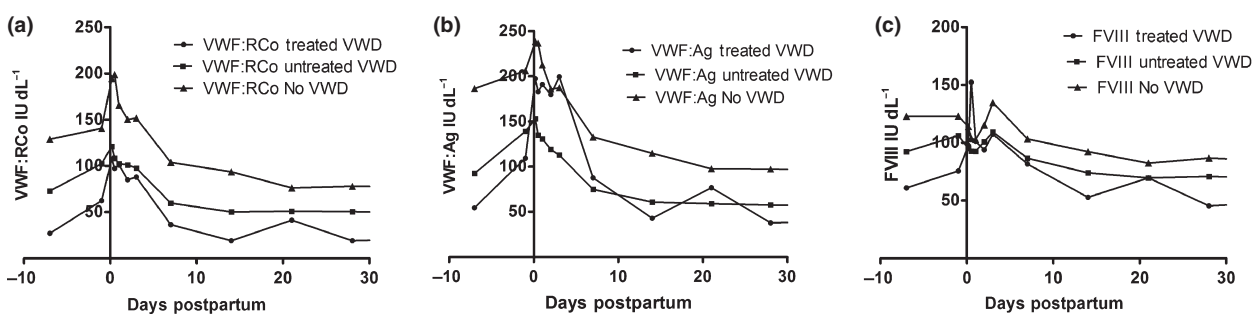

Fig. 4. VWF:RCo, VWF:Ag and FVIII levels among treated subjects compared to levels among women with untreated type 1 VWD and levels among women without VWD.

until 3 weeks postpartum by which time the lochial blood loss was increased compared to that of the other women and at 6 weeks was significantly greater than that of the other women ($P < .01$) (See Fig. 2).

Discussion

We found that VWF levels peaked at 250% of baseline – 12 h postpartum in women with VWD and 4 h postpartum in women without VWD. Levels fell rapidly thereafter, approached baseline by 1 week postpartum, achieved baseline levels by 3 weeks postpartum and remained constant thereafter. Except immediately postpartum when the levels among treated cases were elevated, VWF levels among women with VWD appeared to parallel levels among women without VWD, but were lower at all other time points. Of course, women who were selected for treatment had lower third trimester VWF and FVIII levels than women with VWD who were not treated. Of concern, despite treatment, levels were lowest among those who received treatment. They also had greater estimated blood loss at delivery and greater lochial blood loss late in the puerperium.

Other investigators have recognized that VWF and FVIII peak at the time of delivery [6,7] and begin to fall thereafter. Huq *et al.*, who studied 95 singleton uncomplicated pregnancies and sampled postpartum FVIII and VWF levels during labour and daily for 3 days postpartum, found that the pregnancy-induced increases in FVIII and VWF were maintained for the first 48 h after delivery then levels started to decline on postpartum day 3 [8]. By sampling more often, we found that the levels in the immediate postpartum period remained elevated, while the peak in VWF occurred 12 h postpartum in women without VWD and 4 h in women with VWD. The peak in FVIII occurred on postpartum day 3. Sanchez-Luceros *et al.*, who studied 64 postpartum women, reported that VWF and FVIII return to non-pregnant levels in the late puerperium. In their study, however, only a single postpartum level was obtained 1–3 weeks after delivery. By sampling frequently and serially, we found that VWF and FVIII levels approached baseline within a week and reached baseline by 3 weeks postpartum.

Limitations of the study were partly related to the observational nature of the study; to the requirement for frequent, serial blood sampling; to the setting of recent childbirth; to the fact that VWD is relatively rare; and to the lack of perfect diagnostic tests and assays for VWD. Because 12 blood draws were required and because women were postpartum and sometimes unavailable for testing, not every subject had every assay at every time point. The study relied on the diagnosis, typing and subtyping of VWD performed at the individual centres. Even though all assays of VWF and FVIII for the study were performed at a central laboratory, there was the possibility of variation in preanalytic variables. The sample of VWD subjects was limited by the relative rarity of different subtypes. Only one VWF concentrate was used [Humate-P® (CSL Behring, King of Prussia, PA, USA)], likely because two other products were only recently approved for use in the US. No consistent protocol was followed, treatment varied in intensity and duration and data were not gathered on why a particular regimen was selected. Consequently, the impact of a particular protocol could not be evaluated. Larger studies are necessary to evaluate the impact of other variables such as breastfeeding or mode of delivery on VWF and FVIII levels and on blood loss.

Strengths of the study were the frequent, serial sampling of VWF and FVIII in both women with and without VWD which allowed the construction of curves. It was anticipated that not every subject would get every assay at every time point, so sufficient subjects were recruited and enrolled to achieve a sample size of approximately 20 observations for each assay at each time point. The study was able to elucidate the timing of the fall in VWF and FVIII after childbirth. The study was also able to provide limited data on how women were treated for VWD postpartum. Since the mean EBL and the nadir of the mean haematocrit was the same for untreated women with type 1 VWD as it was for women without VWD, the study provides some justification for the recommendation of refraining from prescribing prophylaxis for women whose third trimester VWF levels are > 50 IU dL^{-1}. Furthermore, anaesthesiologists should be reassured that women whose VWF levels are > 50 IU dL^{-1} in the third trimester will have levels > 50 IU dL^{-1} intrapartum, allowing for the option of regional anaesthesia.

Conclusion

Von Willebrand factor (VWF) levels fall rapidly after delivery. Nonetheless, women with type 1 VWD whose third trimester VWF levels are > 50 IU dL^{-1} do not require treatment. In women who do require treatment, outcomes are not equalized and surveillance for postpartum bleeding by haematologists and obstetrician–gynaecologists is indicated. 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. Women with VWD appear to be at risk of 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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Author contributions

Andra H. James MD and MPH designed the research study, performed the research, analysed the data, wrote the manuscript and approved it. Barbara A. Konkle MD helped design the research study, helped perform the research, contributed to the manuscript and approved it. Peter Kouides MD designed the research study, performed the research, contributed to the manuscript and approved it. Margaret V. Ragni MD performed the research, contributed to the manuscript and approved it. Betty Thames RN, BS performed the research, helped analyse the data and approved the manuscript. Sweta Gupta MD helped perform the research, contributed to the manuscript and approved it. Suman Sood MD helped perform the research, contributed to the manuscript and approved it. Susan K. Fletcher PhD helped perform the research, contributed to the manuscript and approved it. Claire S. Philipp MD designed the research study, performed the research, contributed to the manuscript and approved it.

Disclosures

The authors have the additional declarations of interest: Andra H. James MD, MPH – The University of Virginia receives honoraria from CSL Behring for her participation on an advisory board. Barbara A. Konkle MD – Her declared interests include CSL Behring (consultant), Baxter Healthcare (consultant and research support), Octapharma (central laboratory services) and Kendrion (research support). Peter Kouides MD – The Mary M. Gooley Hemophilia Center receives honoraria from CSL Behring and Novo Nordisk for his participation on advisory boards. Margaret V. Ragni MD – She receives research support from CSL Behring and Baxter. Betty Thames RN, BS – performed the research, and helped analyse the data. She has no conflicts of interest to declare. Sweta Gupta MD – None. Suman Sood MD – None. Susan K. Fletcher PhD – None. Claire S. Philipp MD – She receives research support from Baxter.

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