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**A Prospective Study of von Willebrand Factor Levels and Bleeding in Pregnant Women with Type 1 von Willebrand Disease**

Suman L. Sood<sup>1</sup>, Andra H. James<sup>2</sup>, Margaret V. Ragni<sup>3</sup>, Amy D. Shapiro<sup>4</sup>, Char Witmer<sup>5,6</sup>, Rolando Vega<sup>6</sup>, Doug Bolgiano<sup>7</sup> and Barbara A. Konkle<sup>7,8</sup>

<sup>1</sup>Hematology/Oncology, University of Michigan, Ann Arbor, MI; <sup>2</sup>Dept. of OB/GYN, Duke University Medical Center, Durham, NC; <sup>3</sup>Department of Medicine, Division Hematology/Oncology, University of Pittsburgh and Hemophilia Center of Western Pennsylvania, Pittsburgh, PA; <sup>4</sup>Indiana Hemophilia and Thrombosis Center, Indianapolis, IN; <sup>5</sup>Hematology, The Children's Hospital of Philadelphia, <sup>6</sup>University of Pennsylvania, Philadelphia, PA; <sup>7</sup>Bloodworks Northwest and <sup>8</sup>Department of Medicine, Division of Hematology, University of Washington, Seattle, WA.

**Corresponding Author:**

Barbara A. Konkle, M.D.  
Director, Clinical and Translational Research  
Bloodworks Northwest

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921 Terry Avenue, Seattle, WA 98104

e-mail: BarbaraK@BloodworksNW.org

phone: 206.689.6191

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Women with von Willebrand disease (VWD) are at increased risk of pregnancy-related bleeding, including postpartum hemorrhage (PPH) compared to women without VWD.<sup>1-4</sup> In healthy women without VWD, levels of VWF and FVIII increase 2-4 fold during pregnancy, peaking within 24 hours postpartum, and decrease to baseline levels by one month postpartum.<sup>5-7</sup> Type 1 VWD, accounting for approximately 80% of patients with VWD, is characterized by a parallel deficiency of von Willebrand factor antigen and activity. In cross-sectional analyses of values in women with type 1 VWD, levels of VWF and FVIII also increase during pregnancy, usually to within the normal range.<sup>8,9</sup> Prospective analyses of levels in women with VWD in the peripartum period show that levels peak early after delivery and return to baseline by approximately 3 weeks postpartum.<sup>10,11</sup> Longitudinal data evaluating changes earlier in pregnancy are lacking.

The goal of this study was to model changes in VWF levels during and up to 6 weeks postpartum in women with type 1 VWD, and correlate findings with blood loss. A secondary goal was to identify potential predictors of bleeding with delivery in women with type 1 VWD.

Women with type 1 VWD, defined as at least one value of VWF antigen (VWF:Ag) or VWF activity (VWF:Act) < 50%, VWF Act/Ag > 0.7, and compatible history of mucosal bleeding pre-pregnancy, age 18 or older, were recruited prior to 36 weeks gestation. The study was

terminated early due to low enrollment. Women with a twin gestation, additional bleeding disorder, or use of anti-coagulant or anti-platelet therapy were excluded. All subjects gave written informed consent before enrollment, and the study was IRB approved at each participating institution.

Baseline data included demographics, bleeding symptoms, a modified bleeding score<sup>12</sup> and prior history of PPH, if any. Data collected at time of labor, 24-48 hours, 48 hours-1 week, 1-2 weeks and 6 weeks postpartum included method of delivery, complications, estimated blood loss (EBL), need for hemostatics or blood products and bleeding or VWD diagnosis in the infant. FVIII, VWF:Ag, and VWF:Act were obtained monthly after enrollment, at presentation in labor, and postpartum (12, 24, 48 hours and 1, 2, and 6 weeks). Cord blood was obtained at the time of delivery. Platelet-poor plasma was prepared locally from all samples (3.2% Na Citrate anticoagulation) within 3 hours of collection, frozen at -80°C, and assayed centrally [one-stage Factor VIII activity (MDA 180, Platelin L activator, BioMerieux, Durham, NC), VWF:Ag and VWF:Act by ELISA (American Biochemical and Pharmaceuticals Ltd, Epsom, Surrey, UK)]

Univariate analyses were carried out with the student *t*-test and chi-square test to compare the difference in continuous and categorical variables, respectively. Change in VWF:Ag levels during gestation and postpartum was modeled using longitudinal regression analysis. A mixed-effects exponential growth model was used in the gestational period and an exponential decay model was used in the postpartum period. All analyses were performed using either R version 2.12 (R Foundation for Statistical computing, Vienna, Austria) or Stata 12 (StataCorp, College Station, TX).

Twelve women were recruited from four institutions, with a median age of 31.3 years (range, 19-43). All were Caucasian of non-Hispanic ethnicity. One patient dropped out at 21 weeks gestation. Most were blood type O (67%) and 5/12 (42%) were nulliparas. Three subjects reported prior PPH (27%). The mean baseline bleeding score was 8 [standard deviation (SD) 7]. Mean weeks gestation at delivery was 39 (SD 1), with 2 Cesarean deliveries (18%). Seven women (64%) used epidural anesthesia, and 1 woman each used spinal, general, local, or no anesthesia. Seven women (64%) suffered some degree of genital tear. Mean EBL was 528 ml

(SD 354). One woman experienced immediate PPH, ascribed to uterine atony and requiring a 2 units RBC transfusion, and one woman had secondary PPH at 48 hours and self-treated at home with intranasal desmopressin. Three women were treated with VWF concentrate peri- and postpartum, one for a history of PPH, one for low VWF levels, and the third for unclear reasons. None of the women required readmission, ICU stay, or invasive procedures to stop bleeding.

Mean VWF:Ag, VWF:Act, and FVIII levels at baseline, at presentation in labor and 6 weeks postpartum are shown in Table 1. VWF:Ag and VWF:Act levels correlated well throughout for each woman ( $r$  0.91,  $p < 0.01$ ). The rate of change of VWF levels was heterogeneous and varied individually, with differences between VWF:Ag value at baseline vs. labor ranging from 43-164% and from labor vs. 6 weeks postpartum 21-128% (Figure 1).

During the gestational period, a mixed-effects exponential growth model best fit the rise in VWF:Ag level at labor relative to pre-pregnancy,  $VWF:Ag = \exp(0.028 \times \text{gestational age in weeks})$ , SD 0.007. In this model, VWF:Ag is predicted to double from 19 weeks upwards and some individuals would not double prior to entering labor ( $R^2_{LR} = 0.58$ ). Postpartum, an exponential decay model was fit to the decline in VWF:Ag from labor to 2 weeks PP,  $VWF:Ag = \exp(-0.40 \times \text{gestational age in weeks})$ , SD 0.19 ( $R^2 = 0.79$ ). This model predicted VWF:Ag levels should return to baseline by mean 3.8 weeks (SD 2.6) postpartum. Poor fit of the exponential decay model in the 2-6 week postpartum time period suggests that after 2 weeks postpartum, decay in VWF:Ag is no longer exponential. Modeling results were similar if VWF:Act was used. In the study by James and colleagues, which elucidated the changes in VWF levels postpartum in more detail, VWF levels decayed rapidly and approached baseline at 1 week and then more slowly reached baseline levels at 3 weeks,<sup>11</sup> consistent with our findings.

Using cross-sectional analyses, Cadroy and colleagues modeled changes in VWF:Ag levels during normal pregnancy over 5-39 weeks gestation.<sup>9</sup> They also used an exponential growth model to fit their independent VWF:Ag measurements, which was expressed as  $VWF:Ag = 6.39 \times \exp[0.017 \times \text{Gest.Age(wks)}]$ . Cadroy's estimates of VWF:Ag changes in non-VWD women (0.017) were at the low end of growth rate estimates from our model of type 1 VWD women

(0.016-0.039), suggesting that VWF:Ag levels change more dynamically during pregnancy in women with type 1 VWD than in normal women.

Increased EBL was associated with cesarean delivery ( $r$ ,  $p$ -value; 0.76, 0.02) and manual placenta delivery (0.76, 0.02). Increased hemoglobin loss from 36 weeks gestation to 24 hours postpartum correlated with episiotomy (0.75, 0.03) and degree of tear (0.99, 0.02). Most tears were minor (mean degree 2 (range 1-3)). No significant correlation was found with VWF levels at labor or bleeding score. The woman who bled during delivery had the highest peak VWF levels in the study (VWF:Ag 215% and VWF:Act 183% at labor presentation) and uterine atony, the most common cause of primary PPH.

Hemostatic outcomes and VWF levels were recorded in the neonates born to the study subjects. All were within adult normal ranges and did not correlate significantly with maternal levels at labor or baseline (Table 1). Based on the presumed autosomal dominant inheritance pattern of type 1 VWD there is a 50% chance of having an affected child. In general it is assumed that neonates with type 1 VWD have elevated levels at birth secondary to the stress of birth and should not experience hemorrhage with hemostatic challenges. In our study no infants had bleeding symptoms, were diagnosed with VWD, or bled with procedures (0/3; 1 circumcision, 2 blood draws) in the first 6 weeks of life. We did not have IRB approval to follow the infants further.

We did not perform VWF mutation analysis in our patients. If performed in a larger number of women with VWD, such analyses might help explain the observed heterogeneity in responses. Type 1 VWD results from mutations that affect VWF synthesis, processing and/or secretion.<sup>14,15</sup> It would follow that some defects may suppress or prevent expression of pregnancy-related increases.

The major limitation of our study is the small number of patients enrolled. Compounding this is the fact that type 1 VWD is a heterogeneous disease with a wide variety of genotypes and phenotypes. Our definition of type 1 VWD was liberal with a baseline VWF: Ag or Act < 50%, and inconsistent with NHLBI recommendations of values < 30%.<sup>13</sup> Nevertheless, we also required a history of excessive mucosal bleeding, substantiated by the women's elevated

bleeding scores. Despite these limitations, the strengths of our study include its prospective nature and close follow up, with chart-verified obstetric data and lack of dependence on patient recall.

In conclusion, women with type 1 VWD have highly individual and heterogeneous rates of rise and decline of VWF levels during gestation and postpartum. An exponential growth and decay model was fit to the VWF:Ag peripartum levels up to 2 weeks postpartum. In our study VWF levels were not correlated significantly with blood loss, although, of note, all subjects' VWF levels were >50% at the time of delivery. The children born to study subjects had normal FVIII and VWF levels and did not have bleeding complications. While this study is small and the population homogenous, it confirms the variable rise and fall in VWF levels, and supports the practice of assessing factor levels in women with VWD during pregnancy.

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### **Author contributions**

BAK conceived the original study question. SLS, AHJ, CW and BAK designed the study. MR, RV and AS were instrumental in recruiting subjects. SLS and DB performed primary data analysis, with modeling performed by DB. All authors had access to data. SLS and BAK wrote the manuscript, with substantial input and modification from the other authors.

### **Disclosures**

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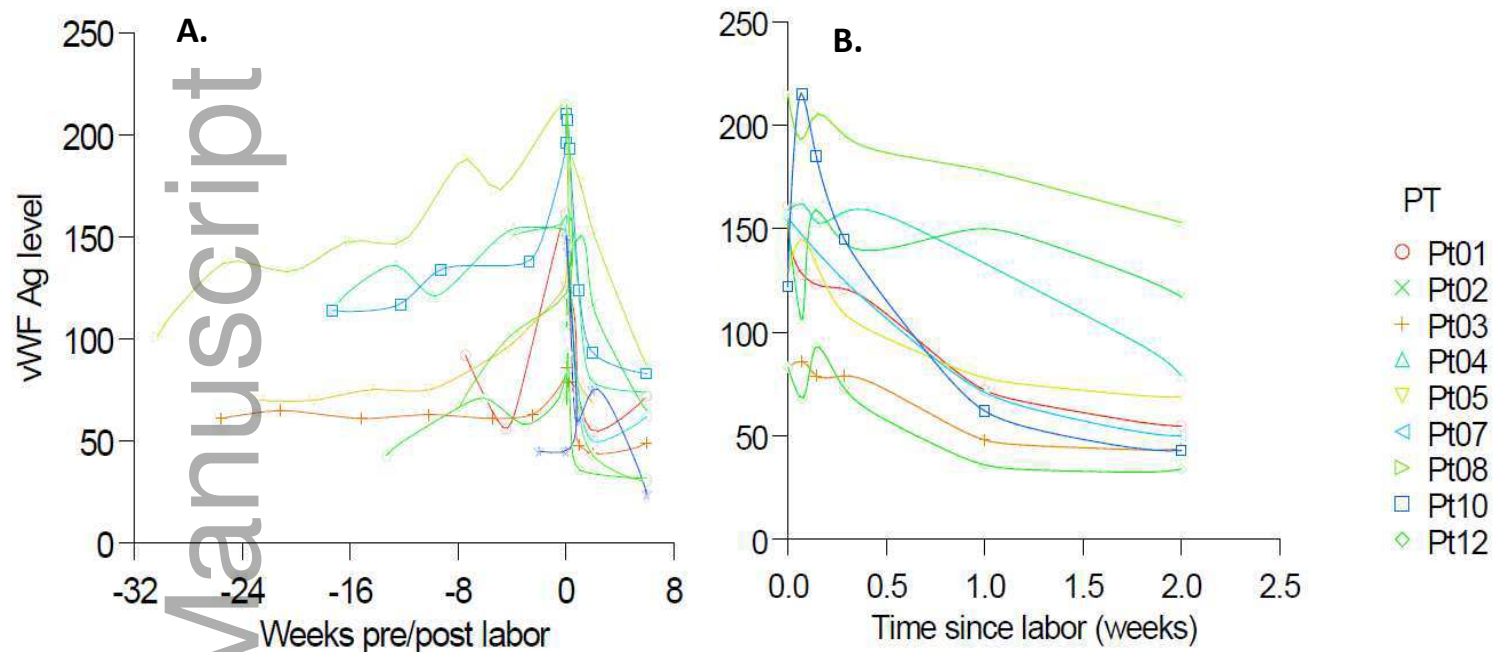
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Table 1: VWD Laboratory Parameters\* over Time

	<b>n</b>	<b>% VWF:Ag (SD)</b>	<b>% VWF:Act (SD)</b>	<b>% FVIII (SD)</b>
Baseline	11	41.1 (7.1)	34.4 (8.4)	76.4 (70.8)
Labor	11	136.4 (50.8)	128.9 (47.8)	134.2 (42.7)
6 weeks PP	10	57.8 (22.8)	52.1 (25.4)	80.9 (32.2)
Infant cord blood	9	97.9 (35.8)	96.2 (34.8)	67.7 (22.6)

\*Values shown are mean [standard deviation (SD)]





**Figure 1. von Willebrand Factor Antigen (VWF Ag) Levels Prior to and Following Labor.** Women with a VWF:Ag <50% prior to pregnancy had VWF:Ag levels measure at time points prior to, at presentation in labor and postpartum (A). Values drawn during the first 2.5 weeks postpartum are shown in B.