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Full Length Article

Feasibility of the Von Willebrand disease PREVENT trial☆

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ABSTRACT

Background: Despite treatment, women with von Willebrand disease (VWD) have lower von Willebrand factor (VWF) levels and greater blood loss at delivery than controls. Current weight-based dosing does not account for the ~1.5-fold increase in blood volume in pregnancy.
Methods: To evaluate the feasibility of a trial to prevent postpartum hemorrhage (PPH), we reviewed pre-pregnancy and 8th month VWF levels in women with VWD with and without PPH following vaginal delivery, assessed VWF concentrate use at delivery by U.S. hemophilia treatment center physician survey, and reviewed thrombosis risk with VWF concentrate by literature review. We determined trial interest and acceptability by structured interviews of physicians and patients. Analysis was by Student's *t*-test for continuous data, and chi-square or Fisher's exact test for discrete data.
Results: PPH was associated with lower pre-pregnancy VWF:RCo, $p < 0.005$; higher pre-pregnancy, 8th and 9th-month weight, each $p < 0.001$; a family bleeding history, $p = 0.036$; and VWF concentrate treatment, $p = 0.005$. Surveyed physicians reported first-line therapy at delivery was VWF concentrate, at a mean dose 50 IU/kg. A trial of a 1.5-fold volume-based dose increase was acceptable to physicians and patients, if it is safe and if costs and visits are minimized. A literature review determined thrombosis risk with VWF concentrate is low, 0.4%.
Conclusions: This study suggests pre-pregnancy VWF:RCo may predict PPH, but 50–80 IU/kg VWF concentrate dosing may not prevent PPH. If pharmacokinetic modeling confirms volume-based dosing achieves VWF levels comparable to pregnant controls, it may be possible to determine if volume-modified VWF concentrate dosing will reduce PPH in VWD.

1. Introduction

Postpartum hemorrhage (PPH), defined as ≥500 cm^3 blood loss in the first 24 h following vaginal delivery, complicates 6% of pregnancies in women with von Willebrand disease (VWD) [1,2], and is associated with greater morbidity, longer length of stay, and greater transfusion requirement than in women without VWD [3–6]. A recent prospective observational study of women with VWF levels <50 IU/dl at delivery indicated that, despite treatment at delivery, VWF:RCo levels were 1.4-fold lower and postpartum blood loss was 1.5-fold greater than in healthy pregnant controls [7]. These findings, confirmed in a subsequent retrospective survey [8], suggest that regimens may be insufficient to prevent postpartum bleeding [9–12]. Plasma-derived von Willebrand factor (pdVWF) is the current drug of choice at delivery in women with VWD, and is recommended over desmopressin (DDAVP) which may be complicated by hyponatremia and seizures [13,14]. VWF concentrate dosing at delivery, 50 IU/kg, per expert opinion [15], is 1.5-fold lower than the dose recommended for surgery, 80 IU/kg [10], and thrombotic risk at delivery is a concern [16]. Further, dosing is calculated by body weight rather than blood volume, which increases 1.5-fold during pregnancy [17–20], despite the precedent in children for higher factor dosing due to their higher blood volume than adults [21,

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22]. Thus, the optimal treatment of women with VWD at delivery is unknown, specifically, whether higher doses of plasma-derived (pdVWF) or similar or higher doses of recombinant VWF (rVWF) concentrate (*Vonvendi®,* rVWF), an FDA-approved drug with greater purity and more hemostatic ultra-large VWF multimers [23], will effectively prevent PPH. We, therefore, conducted preparatory work, The Feasibility Study, to determine the feasibility of a phase III randomized clinical study to reduce PPH in women with type 1 or type 2 VWD.

1.1. The PREVENT PPH trial

The PREVENT PPH trial, originally developed as a trial concept for the Hemophilia and Von Willebrand Disease Subcommittee of the 2009 National Heart, Lung, and Blood Institute (NHLBI) State of the Science (SoS) Symposium [24], is a prospective, randomized phase III multi-center trial to test the hypothesis that rVWF concentrate will more effectively reduce PPH than pdVWF in women with type 1 and type 2 VWD. The dose will be derived from PK-modeling to simulate up to 1.5-fold higher VWF concentrate dose based on blood volume changes in pregnancy [17–20], i.e. 50 IU/kg pdVWF with 50 IU/kg or 80 IU/kg rVWF or ~1.5-fold higher, up to 120 IU/kg (Fig. 1). The primary endpoint will be estimated blood loss (EBL) at 24 h postpartum, measured by pictorial blood assessment chart (PBAC) [25,26] modified for use in the postpartum setting [7]. Secondary outcomes will include postpartum cumulative blood loss by PBAC over 42 days. A sample size of 90 (45 per arm) will provide 80% power to detect a 29% reduction or a 1.4-fold reduction in EBL at delivery, using a two-sided test with $\alpha = 0.05$, a clinically relevant reduction, given the 1.4-fold greater EBL in the James study [7].

1.2. The feasibility study

The Feasibility Study, developed as preparatory work for the PREVENT PPH trial, included 1) a retrospective observational study of factors associated with PPH in women with VWD; 2) a review of VWF dosing at delivery by sites participating in the James study [7]; 3) a literature review of thrombosis associated with plasma-derived VWF (pdVWF) and recombinant VWF (rVWF) concentrates; 4) a physician survey to determine current treatment practice in VWD deliveries; and 5) structured interviews of HTC physicians and VWD patients to determine trial acceptability.

2. Methods

To establish trial feasibility, we 1) compared pre-pregnancy and 8th month VWF levels in women with type 1 or 2 VWD followed at the Hemophilia Center of Western PA (HCWP) and PPH (≥500 cm^3 blood loss in 1st 24 h postpartum) and without PPH (<500 cm^3 blood loss) following vaginal delivery; 2) collected data on VWF concentrate dosing at delivery from sites participating in the James study [7]; 3) assessed thrombosis risk and VWF concentrate dose by literature review; 4) surveyed U.S. hemophilia treatment center (HTC) physicians on current practice regarding VWF concentrate at delivery; and 5) conducted structured interviews of 18 physicians and 18 VWD patients to determine trial acceptability.

2.1. Statistical methods

Means ± standard deviations and frequencies (percentages) are presented. Characteristics among women with and without PPH, defined as ≥500 cm^3 blood loss at vaginal delivery, were compared using Student's *t*-test for continuous data and chi-square or Fisher's exact test for discrete data. The correlation between the pre-pregnancy bleeding score and the estimated blood loss at the time of delivery was computed. A *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Retrospective study of postpartum hemorrhage

In a retrospective chart review of 16 women with VWD cared for at HCWP, we identified 14 type 1, defined as VWF:RCo <0.50 IU/ml, and 2 type 2 patients, cared for at HCWP, who underwent vaginal delivery. Of these, eight experienced a postpartum blood loss of <500 ml (no PPH) and eight experienced a postpartum blood loss of ≥500 ml (PPH) (Table 1). These 16 represented all women on whom peripartum records were available. As compared to those with no PPH, women with PPH had significantly lower pre-pregnancy VWF:RCo, 0.34 IU/ml vs. 0.48 IU/ml, but similar 8th month VWF:RCo, 1.32 IU/ml vs. 1.45 IU/ml, $p = 0.484$; and significantly higher weight pre-pregnancy, 88.1 vs. 67.6 kg; at the 8th month, 99.9 vs. 75.0 kg, and at delivery: 104.0 vs. 78.6 kg, all $p < 0.005$. They were also more likely to have a family bleeding history, 75.0% vs. 12.5%, $p = 0.041$, and to be treated with VWF

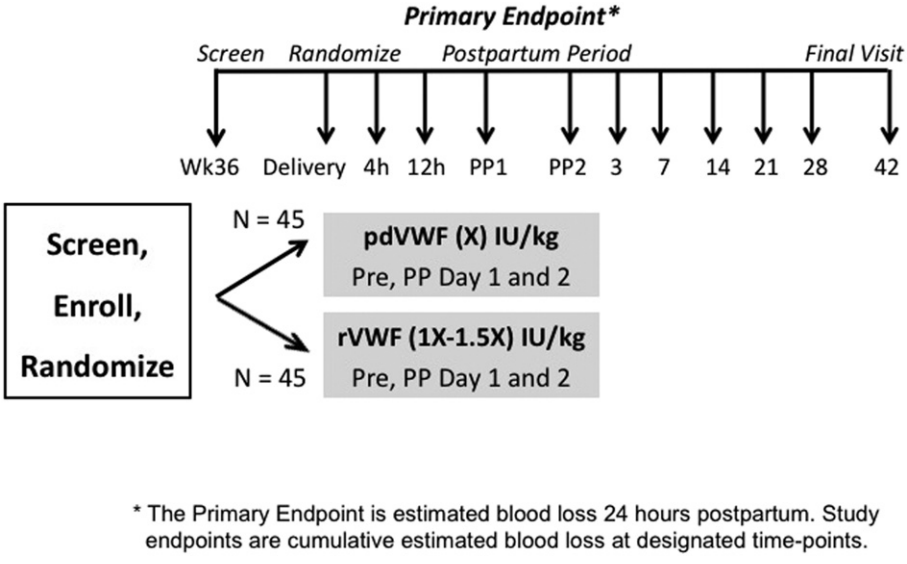

Fig. 1. Schema for the PREVENT Postpartum Hemorrhage (PREVENT PPH) Trial. The schema for the proposed PREVENT PPH trial will compare baseline VWF concentrate dose, X, e.g. 50–80 IU/kg, with a 1.5-fold higher dose, 1.5×, e.g. 80–120 IU/kg, to be determined (in parentheses) by pharmacokinetic simulation and modeling based on pregnancy-associated blood volume increases, to reduce postpartum blood loss. The six post-partum time points will include one in-person visit and five phone-call visits. Pre = pre-partum, PP = postpartum.