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ORIGINAL ARTICLE

Primary postpartum hemorrhage in women with von Willebrand disease and carriers of hemophilia: a retrospective analysis

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Abstract

Background: Between 2002 and 2011, the incidence of severe primary postpartum hemorrhage (PPH) in Dutch women with von Willebrand disease (VWD) and hemophilia carriers (HCs) was 8% vs 4.5% in the general population.

Objectives: To determine the contemporary incidence of severe primary PPH in women with VWD and HCs.

Methods: All women with VWD or HCs who delivered between 2012 and 2017 were selected from all 6 Dutch hemophilia treatment centers. Data on patient and disease characteristics, peripartum hematologic and obstetric management, and outcomes were retrospectively collected. Incidence of severe primary (≥1000 mL of blood loss ≤24 hours after childbirth) and primary (≥500 mL within ≤24 hours after childbirth) PPH was compared with the (1) previous cohort and (2) general Dutch population and between (3) women with VWD and HCs with third-trimester coagulation activity levels

<50 international units (IU)/dL vs ≥50 IU/dL and (4) women treated with vs without peripartum hemostatic prophylaxis.

Results: Three-hundred forty-eight deliveries (151 VWD, 167 hemophilia A, and 30 hemophilia B carriers) were included. The severe primary PPH incidence was 10% (36/348) and remained stable over time, whereas this incidence has increased in the general population (to 8%), leading to a similar risk (P = .17). Severe primary PPH risk was comparable between women with coagulation activity levels <50 and ≥50 IU/dL (11% [7/66] vs 10% [29/279]; odds ratio, 1.02; 95% CI, 0.43-2.44) and comparable between those with and those without prophylaxis (12% [11/91] vs 10% [25/254]; odds ratio, 1.26; 95% CI, 0.59-2.68).

Conclusion: Severe primary PPH in women with VWD and HCs remained stable and is comparable with the increasing prevalence in the general population. More research is needed to find the optimal pregnancy management strategy for safe delivery in VWD and HC.

KEYWORDS
hemophilia A, hemophilia B, postpartum hemorrhage, pregnancy, von Willebrand diseases

Essentials

- Bleeding disorders increase the risk of severe postpartum bleeding (PPH).
- The PPH incidence in women with von Willebrand disease and hemophilia carriers was compared with that in the Dutch population.
- One in 10 women with these disorders develop PPH, which appears to stabilize over time.
- The PPH incidence was comparable with the increased incidence in Dutch women.

1 | INTRODUCTION

von Willebrand disease (VWD) and hemophilia are the most common inherited bleeding disorders. Women with these disorders are at increased risk of postpartum hemorrhage (PPH) compared with the general population [1–3]. PPH remains one of the main causes of serious maternal morbidity and mortality; thus, careful peripartum management for women with VWD or hemophilia carriers (HCs) is of great importance [4,5]. In accordance with many high-income countries, a rise in PPH has been noticed in the general Dutch population. Taking into account the PPH definition of ≥1000 mL blood loss used in the Netherlands, the incidence (6.4% in 2014) is relatively high compared with that in Norway (1.1%) and the United States (4.1%-5.1%) and relatively low compared with that in Australia (4.7%-10.7%) [6]. Worldwide, it is estimated that about 14 million women experience PPH each year and that PPH accounts for 27% of all maternal deaths. Only recently the World Health Organization recommended in favor of objective measurement of postpartum blood loss to improve the detection and treatment of PPH in women experiencing vaginal birth overestimation of blood loss [7].

Pregnancy induces a procoagulant state, which might not occur to the same extent in women with inherited bleeding disorders [8–12]. Peripartum prophylactic management for these women combines hematologic and obstetric strategies. Hematologic prophylactic management mainly aims to correct the quantitative (VWD type 1 and 3) or qualitative (VWD type 2) abnormalities of von Willebrand factor (VWF) in women with VWD. Likewise, in HCs, deficiencies in factor (F) VIII (hemophilia A, but also in VWD) or FIX (hemophilia B) are targeted [13]. International guidelines, at the time of this cohort study, were based on expert opinion and advised to reduce the PPH risk by increasing the peripartum clotting factor activity levels by administering clotting factor concentrate or desmopressin [14]. These guidelines recommended prophylaxis if third-trimester clotting factor activity is below 50 international units (IU)/dL; however, optimal obstetric and hematologic peripartum management to decrease PPH risks remains unclear [15]. The most recent evidence-based guideline on VWD highlights the need for more research on the prevention of PPH in VWD [16].

A historic retrospective cohort study in 3 Dutch hemophilia treatment centers (HTCs) reported a severe primary PPH prevalence of 8% in women with VWD and HCs between 2002 and 2011 vs 4.5% in the general population [17]. International evidence subscribed the high risk for PPH in women with these bleeding disorders [15,18]. Therefore, the national Dutch guideline increased cutoff clotting factor activity levels to commence prophylactic hemostatic treatment to 80 IU/dL and increased target activity levels to 150 IU/dL at delivery. In 2017, the prospective Dutch pregnancy in inherited bleeding disorders study commenced to analyze the PPH incidence in women with VWD and HCs after

implementation of the revised national guidelines. The current retrospective study included the period preceding this revision and is aimed to determine the incidence of severe primary PPH and primary PPH, between 2012 and 2017, in relation to third-trimester clotting factor activity level and hemostatic obstetric management, both in women with VWD and HCs, in comparison to the general population.

2 | METHODS

2.1 | Study design and patients

We conducted a retrospective cohort study in all 6 Dutch HTCs, covering 8 hospitals. These centers followed the former national Dutch guidelines for peripartum management, recommending peripartum prophylactic treatment with clotting factor concentrates if third-trimester clotting factor levels of FVIII, FIX, and VWF activity and antigen level are <50 IU/dL to reach target levels of ≥100 IU/dL with clotting factor concentrate [19]. Ethical approval was obtained at each center. Eligible deliveries were deliveries from women with an established diagnosis of hemophilia A or B carriership (based on the genetic diagnosis) or VWD (ie, a documented lowest VWF ristocetin or activity level <50 IU/dL) registered at an HTC between January 1, 2012, and December 31, 2017. VWD subtype 1, 2, or 3 was derived from the medical files, no reclassifications were performed. Deliveries were excluded if women had received multiple diagnoses of bleeding disorders or if no information on peripartum blood loss was provided. Women who were counseled but who delivered at non-HTCs were excluded beforehand, due to lack of data. Eligible women were selected through analysis of the hospitals patient registry, by searching laboratory reports, hospital discharge letters and hospitals' medical file databases.

2.2 | Data collection

Patient and disease characteristics, peripartum hematologic and obstetric management and outcomes were collected from the patient medical files. The primary outcome parameters were severe primary PPH, defined as ≥1000 mL of blood loss from the genital tract ≤24 hours after childbirth, and primary PPH, defined as ≥500 mL of blood loss within 24 hours after childbirth. Secondary PPH was defined as blood loss from the genital tract between 24 hours and 3 months after childbirth [20]. Peripartum blood loss is routinely based on visual estimation but weighted once excessive blood loss is impending. In case peripartum blood loss was not specified in milliliters but was deemed as being normal, it was noted as <500 mL, or when labeled as abnormal, it was noted as ≥500 to 1000 mL (primary PPH). Peripartum management included prophylactic treatment (clotting factor concentrates, desmopressin and tranexamic acid), mode of delivery and perineal status (episiotomy vs perineal laceration). Obstetric preventive measures included oxytocin administration. Patient and disease characteristics include baseline factor activity levels, third-trimester factor activity levels, and peripartum factor activity levels. These factors include VWF antigen levels, VWF activity levels, FVIII activity levels, and FIX activity levels. In case third-trimester factor activity levels were not determined, but second trimester levels were ≥50 IU/dL, the third-trimester levels were categorized as ≥50 IU/dL. Other pregnancy and peripartum characteristics included prenatal diagnostics and neuraxial techniques.

The local PPH prevention and treatment guidelines from each hospital were obtained for comparison. Data on the following obstetric risk factors for PPH were collected: uterus atony, retained placenta, cesarean section (CS), instrumental delivery, shoulder dystocia, prolonged third stage of labor, induction of labor, augmentation of labor, preeclampsia, episiotomy, perineal laceration, nulliparity, multiple gestation, age >35 years, and placenta previa. Occurrence of PPH and obstetric risk factors in the general population during the same time period were retrieved from the Dutch National Perined database for comparison [21]. Perined is a national registry containing routinely collected data on pregnancy and pregnancy outcomes. This registry covers 97% of all Dutch deliveries [21]. Primary PPH (500-1000 mL), uterus atony, preeclampsia, and prolonged third stage of labor are not recorded in this database, blood product use and lacerations are inaccurately recorded.

2.3 | Statistical analysis

IBM SPSS Statistics version 25 (IBM Corp) was used for statistical analyses. Descriptive analyses consisted of mean and SD or median with 95% CIs depending on the distribution for continuous variables and numbers and percentages for categorical variables. Logistic regression with reporting of the odds ratio (OR) and 95% CI was used to assess the relation between third-trimester clotting factor activity levels or prophylactic treatment and severe primary PPH. To determine the influence of obstetric risk factors and type of bleeding disorder on PPH, the incidence of these factors in the non-PPH and PPH group of this cohort, in the general population, and in the study by Stoof et al. [17] were compared by descriptive statistics. Furthermore, the CS rate and severe primary PPH incidence between (1) women who chose prenatal diagnostics for male fetuses regarding hemophilia or fetuses with specific types of VWD and those who opted out of prenatal diagnostics and between (2) induced and spontaneous deliveries were compared. Severe primary PPH in women according to perineal status was assessed and compared to the general population. All analyses were repeated for primary PPH (Supplementary Table S1). Lastly, incidence of anesthetic procedures in this study cohort was compared to the general population.

3 | RESULTS

3.1 | Participant selection and characteristics including neonatal outcome

Overall, 292 eligible women were identified encompassing 348 deliveries in the 6 HTCs (Tables 1 and 2). The median number of

TABLE 1 Characteristics of study population (*N* = 292 women).

Characteristic	Deliveries (*N* = 348)
Age at delivery (y)	31 (28-34)[a]
Primipara	141 (40.5)
Ethnicity	Dutch
No. of deliveries per woman	
1	237 (81.2)
2	54 (18.5)
3	1 (0.3)
Mode of delivery	
Spontaneous vaginal delivery	269 (77)
Assisted vaginal delivery	14 (4)
Cesarean section	65 (19)
Elective	26 (7)
Emergency	39 (11)
Neonatal morbidity	
Cephalohematomas	3 (0.8)
Intracranial hemorrhages	0 (0)
Neonatal deaths	0 (0)

[a]Data are presented as *n* (%) or median (25th-75th percentile).

deliveries per hospital was 42 (IQR, 26.5-59.5). Most women were either HA carriers (*n* = 146, 50%) or women with VWD type 1 (*n* = 95, 33%). During the study period, 81% (237/292) of women delivered once. The mode of delivery was a spontaneous vaginal delivery in 77% (269/348), assisted vaginal delivery in 4% (14/348; all vacuum-assisted delivery), and a CS in 19% (65/348: 26 elective and 39 emergency). All assisted vaginal deliveries consisted of pregnancies where fetuses were either female (*n* = 7, HA or HB), unaffected neonates (2 confirmed by prenatal diagnostics), or maternal mild VWD type 1 (*n* = 5). Median duration of hospitalization was 48 hours (IQR, 24-77).

One pregnancy was started by in vitro fertilization after preimplantation genetic testing. Prenatal diagnosis was performed in 97 pregnancies, and affected neonates were confirmed in 55% (53/97). A total of 359 neonates were born. One intrauterine fetal death occurred at 28 weeks of gestation. Three (1%, 3/359, 2 HA and 1 HB) cephalohematomas were reported. No intracranial hemorrhages or neonatal deaths occurred.

3.2 | PPH prevalence and relation to prophylactic treatment

Overall, severe primary PPH occurred in 10% (36/348) of deliveries and primary PPH in 28% (99/348) of deliveries (Table 2). Besides the single VWD type 3 case with severe primary PPH, deliveries of women with VWD type 2 had the highest incidence of severe primary PPH (18%, 6/34) as well as the highest primary incidence of PPH (50%, 17/34). In comparison with the previous cohort study by Stoof et al. [17], there was no difference in severe primary PPH incidence of 8% (14/185) (*P* = .30) or primary PPH 34% (62/185) (*P* = .22). Similarly, compared to the general population, severe primary PPH occurred as often as in our cohort 8% (57159/743.591, *P* = .17) of deliveries (primary PPH not being recorded in Perined). Secondary PPH was neither recorded in the electronic patient files for the study population nor recorded in Perined database and therefore could not be assessed.

Prophylactic treatment consisted of clotting factor concentrates in 59 deliveries and desmopressin in 29 deliveries (hemophilia A, *n* = 16; VWD, *n* = 13). Tranexamic acid was administered during 36% (125/223) of deliveries. Prophylactic treatment was provided in 96% (63/66) of women with third-trimester factor activity levels <50 IU/dL. Independent of prophylactic treatment, the severe primary PPH incidence in women with third-trimester levels <50 IU/dL was comparable with that in women with third-trimester clotting factor levels ≥50 IU/dL (11% [7/66] vs 10% [29/279]), without significant confounding by diagnosis VWD vs carrier (OR, 1.63; 95% CI, 0.46-5.80, with third-trimester levels <50 IU/dL as reference category; Table 2). Contrarily, the primary PPH incidence in women with third-trimester levels <50 IU/dL was higher than that in women with third-trimester clotting factor levels ≥50 IU/dL (40.9% [27/66] vs 25.4% [71/279]) but was comparable when corrected for prophylactic treatment (OR changed from 2.02 [95% CI, 1.16-3.55] to 1.30 [95% CI, 0.55-3.09], with third-trimester level ≥50% as the reference category; Supplementary Table S1). This result did not change after correcting for diagnosis VWD vs carrier (OR, 1.20; 95% CI, 0.50-2.88).

3.3 | PPH risk factors, management, and outcome

The incidence of PPH risk factors in our study population was comparable to the general population (Table 3). As can be expected, PPH ≥500 mL occurred more often in women with VWD compared to HCs (36% vs 23%; OR, 1.88; 95% CI, 1.18-3.01). Obstetric risk factors were assessed within the PPH and no PPH group (Supplementary Table S2). The most common risk factors, uterus atony, retained placenta, and CSs, were clearly associated with PPH (Table 3). The severe primary PPH incidence was similar in primiparous and multiparous women (Supplementary Table S3).

Local obstetric guidelines to manage PPH were based upon 1 national obstetric guideline. All local guidelines recommend oxytocin administration at 5 IE intramuscularly or intravenously after a vaginal delivery, either administered 5 or 10 IE intravenous after a CS. Criteria to start sulprostone, admission criteria, and time to the operating theater in case of persistent blood loss exposed more heterogeneity and were not described in detail in the different local protocols.

Blood products were administered in 5% (18/348) of deliveries (red blood cells, *n* = 10; platelets, *n* = 8; plasma, *n* = 4). Previously, red blood cell consumption in women with VWD and HCs was reported to be 4% (8/185), thus comparable to our cohort (*P* = .67). Hemostatic

TABLE 2 Postpartum hemorrhage according to bleeding disorder and third-trimester factor level.

	Deliveries *n*	Severe primary PPH *n* (%)	Primary PPH *n* (%)	Estimated blood loss (mL) Median (25th-75th)
Total	348	36 (10.3)	99 (28.4)	300 (200-500)
VWD type 1	116	14 (12.1)	36 (31.0)	350 (200-550)
VWD type 2	34	6 (17.6)	17 (50.0)	475 (300-760)
2A	16	4 (25.0)	9 (56.3)	500 (300-1050)
2B	5	1 (20.0)	3 (60.0)	500 (350-1630)
2M	10	1 (10.0)	4 (40.0)	325 (200-500)
2N	3	0 (0.0)	1 (33.3)	300
VWD type 3	1	0 (0.0)	1 (100.0)	900
Hemophilia A carrier	167	13 (7.8)	34 (20.4)	300 (200-400)
Hemophilia B carrier	30	3 (10.0)	11 (36.7)	400 (200-500)
Factor level in third trimester				
<50 IU/dL	66	7 (10.6)	27 (40.9)	375 (250-600)
Prophylaxis	63	7 (11.1)	27 (42.9)	400 (200-600)
No prophylaxis	3	0 (0.0)	0 (0.0)	350 (300-400)
≥50 IU/dL	279	29 (10.4)	71 (25.4)	300 (200-500)
Prophylaxis	28	4 (14.3)	9 (32.1)	300 (200-500)
No prophylaxis	251	25 (10.0)	62 (24.7)	300 (200-500)
Previous cohort	185	14 (8)[a]	62 (34)	300 (300-400)[b]
General population	743.591	57.159 (8)[a]	NA	NA

Severe primary and primary PPH were defined as ≥1000 mL and ≥500 mL of blood loss from the genital tract within 24 hours, respectively.
NA, not available; PPH, postpartum hemorrhage; VWD, von Willebrand disease.
[a]In comparison with the previous cohort study by Stoof et al. [17], there was no difference in severe primary PPH incidence (8% [14/185] vs 10% [36/348]; *P* = .30) or primary PPH (34% [62/185] vs 28% [99/348]; *P* = .22).
[b]Median and 95% CI.

uterus compression sutures were used 3 times, embolization of the uterine arteries 1 time and 1 woman underwent a hysterectomy to control PPH. No maternal deaths occurred.

Regarding hemostatic treatment, we found that, in severe PPH cases, tranexamic acid and desmopressin were administered more often compared with deliveries with <1000 mL of blood loss (OR, 3.64; 95% CI, 1.77-7.48; and OR, 3.91; 95% CI, 1.58-9.62, respectively). This was not so obvious for clotting factor concentrates (OR, 1.49; 95% CI, 0.68-3.25). In 13 of 36 (36%) deliveries complicated by severe PPH, no tranexamic acid was used.

3.4 | Mode of delivery in relation to prenatal diagnostics

Prenatal diagnostics was performed in 18% (62/348) of pregnancies. The secondary CS rate was 26% (10/38) in pregnancies where prenatal diagnostics had confirmed an affected fetus vs 9% (2/23) in pregnancies where prenatal diagnostics confirmed an unaffected fetus. In women who opted out of prenatal diagnostics, the CS rate was 25% (1/4).

3.5 | PPH and CS in relation to labor induction and augmentation of labor

Induction of labor was performed in 38% (132/348) of deliveries. In case of induced labor, severe primary PPH occurred in 12% (16/133), whereas deliveries with a spontaneous start developed severe primary PPH in 8% (16/191) of cases (OR, 1.5; 95% CI, 0.73-3.14; *P* = .27, adjusted [age, parity, and CS]; OR, 1.5; 95% CI, 0.74-3.29). In the general population, deliveries started with induction, and deliveries with a spontaneous start resulted in an equal severe primary PPH incidence of 8% (14,625/182,951 vs 32,547/420,630).

Deliveries in the current cohort that started through induction resulted in a CS in 17% (22/132) of cases, whereas deliveries with a spontaneous start were converted to a CS in 9% (17/187) of cases (OR, 2.0; 95% CI, 1.02-3.94; *P* = .05, adjusted [age and parity]; OR, 2.0; 95% CI, 1.02-3.94). In the general population, deliveries started with induction resulted in a CS in 15% (34,800/234,250) of cases, whereas deliveries with a spontaneous start ended with a CS in 13% (52,566/417,833) of cases.

Augmentation of labor occurred in 141 deliveries, but this was not associated with a higher severe primary PPH incidence (10% [21/202]

TABLE 3 Postpartum hemorrhage risk factor occurrence in this cohort vs the general population and the previous cohort.

Risk factor	Current cohort (*n* = 348) *n* (%)[a]	General population[b] (*n* = 743.591) *n* (%)[c]	Previous cohort[d] (*n* = 185) *n* (%)[e]
Uterus atony	17 (4.9)	NA	2 (1.2)
Retained placenta	31 (8.9)	28.807 (3.9)	7 (4.0)
Cesarean section	65 (18.7)	169.406 (22.8)	34 (18.8)
Instrumental delivery[f]	14 (4.9)	81.305 (14.3)	14 (9.7)
Prolonged third stage of labor	8 (2.3)	NA	9 (5.1)
Induction of labor[g]	132 (41.0)	225.381 (34.1)	49 (31.2)
Augmentation of labor[g]	140 (43.5)	346.099 (47.7)	31 (19.7)
Episiotomy[f]	68 (24.5)	190.823 (33.2)	51 (36.2)
Perineal laceration[f]	149 (55.0)	221.340 (38.5)	68 (47.6)
Nulliparous	149 (42.8)	376.758 (50.7)	109 (58.9)
Multiple gestation	11 (3.2)	16.754 (2.3)	6 (3.2)
Age >35 y	78 (22.4)	161.368 (21.7)	39 (21.1)

Total N depends on available and relevant data.
NA, not available.
[a]271 to 348.
[b]Data from Perined 2012-2017.
[c]574.185 to 743.591.
[d]Data from Stoof et al. [17] 2007-2011.
[e]141 to 185.
[f]Vaginal deliveries only.
[g]Primary cesarean sections excluded.

vs 11% [15/141]; OR, 0.98; 95% CI, 0.48-1.96). In the general population, deliveries with augmentation resulted in the same severe primary PPH incidence as in those deliveries which progressed naturally: 8% (27,266/346,099 vs 29,893/397,492) of cases.

3.6 | PPH in relation to perineal injury

The episiotomy incidence was 20% (68/342) and perineal lacerations occurred in 44% (149/342). Women with an episiotomy developed severe primary PPH in 15% (9/59) of deliveries, vs 9% (13/149) in case of laceration (OR, 1.60; 95% CI, 0.65-3.94). In women who either had an episiotomy or perineal laceration (217/342, 63%), the severe primary PPH incidence was 10% (22/217) vs 12% (14/118) if no perineal injury occurred (OR, 0.84, 95% CI, 0.41-1.71). In the general population, an episiotomy incidence of 33% (190.823/574.185) is reported, with a severe primary PPH incidence of 10% (18.448/190.823) (P = .42).

3.7 | Anesthesia

Information on anesthesia procedures was available in 92% (321/348) of deliveries. Neuraxial procedures were performed in 36% (116/321) vs 44% (329.273/743.591) in the general population (OR, 0.71; 95% CI, 0.57-0.90; P = .004), whereas no information was provided of the previous cohort by Stoof et al. [17]. Of the nulliparous women of this cohort study, 48% (64/143) women received neuraxial anesthesia, vs 29% (52/178) of multiparous women (general population 53% and 35%, respectively). Alternative anesthetic procedures consisted of 13% (43/321) opioid use and 6% (19/321) general anesthesia, and in 45% (143/321), no anesthetic procedures were performed.

Of the 113 deliveries in women with type 1 VWD, neuraxial anesthesia was performed in 47 (42%), type 2A in 1 of 15 deliveries, type 2B 0 of 5, type 2M 2 of 10, and type 2N 2 of 3. The sole type 3 VWD patient did not receive neuraxial anesthesia. No bleeding complications were recorded after neuraxial anesthesia. We did not record spinal vs epidural technique. Mean third-trimester VWF and FVIII activity levels were higher in women with VWD who underwent neuraxial anesthesia vs other or no anesthesia (mean VWF activity 97.5 vs 67.4 IU/dL and mean FVIII 164 vs 127 IU/dL, $P < .01$).

4 | DISCUSSION

This national retrospective cohort study assessed the PPH incidence in women with VWD and HCs between 2012 and 2017 and is, to our knowledge, the largest cohort study in women delivering with a bleeding disorder. Our results suggest that the prevalence of severe primary PPH has remained constant over time for both women who receive prophylactic treatment and those who do not. This is different from the general population where the incidence of severe primary PPH is increasing and which is now similar to women with VWD and HCs.

The consistent incidence of severe primary PPH in this cohort of women with VWD and HCs over time might be due to the ongoing awareness of the peripartum bleeding risk in this population, whereas the declining primary PPH incidence would support the concept of improved primary PPH preventive strategies. In light of the increasing severe primary PPH incidence in the general population, women with inherited bleeding disorders seem to do quite well. The increase in severe primary PPH in the general population, which has been noticed in multiple high-income countries, has been a topic of discussion [22,23]. At the time of the study of Stoof et al. [17], the estimated severe primary PPH incidence in the general population was 4.5%, but this has now risen to 8%. Studies have investigated which risk factors might have caused this alarming trend [6]. Risk factors include the increasing maternal age, CS rates, increased induction rates, and prolonged second stage of labor [24]. However, these factors are not sufficient in explaining this temporal increase; increased awareness of PPH and improved registration may also play an important role in the increased incidence in the general population. In the Netherlands, a more active third stage of labor, sharpened PPH prevention protocols, and subsequent analysis of PPH cases have become part of the routine care.

Peripartum guidelines for women with inherited bleeding disorders as available during the time of this cohort analysis based on

expert opinion [14,25]. Prophylactic treatment, also during the time period of this cohort study, generally comprises correction of coagulation only when third-trimester clotting factor levels remain <50 IU/dL. Women with low clotting factor activity levels are still at the highest risk of primary PPH, suggesting that higher peripartum trough and peak levels of FVIII, FIX, and VWF during and after delivery may be necessary. This would more adequately meet the much higher peripartum physiological levels seen in women without inherited bleeding disorders [8,12]. In these women, peripartum mean factor activity levels peak with FVIII at 270 IU/dL, FIX at 150 IU/dL, and VWF activity levels at 298 IU/dL [12,26]. Furthermore, the primary PPH incidence in women with clotting factor activity levels ≥50 IU/dL also exceeds the incidence previously reported in the general population. These patients mostly do not receive prophylactic treatment, but their VWF, FVIII, and FIX levels remain under the physiological levels reported in the general population. The PRegnancy and Inherited bleeding DisordErS study study (NTR: NL6770) started in 2017 to prospectively assess PPH in VWD and HCs after the revision of the national Dutch guideline with increased cutoff for clotting factor activity levels to commence prophylactic hemostatic treatment and increased target activity levels at delivery. Hopefully, this study will provide more information on the effects of increasing clotting factor levels on PPH incidence.

Important topics during prenatal counseling include prenatal diagnostics, induction of labor, and CS chances. Opting out of prenatal diagnostics appears to be associated with a slight increase in CS rate. A secondary CS is more likely in case of an (potentially) affected child, contrary to being assured of an unaffected status. This finding underlines the importance of knowing fetal status during delivery. Induction of labor could aid in pregnancies where prophylactic treatment and distance to the hemophilia treatment and comprehensive care center are an issue in light of the PPH risk. A recent qualitative study has indicated that home-hospital distance caused worry in HCs [27]. The choice in both prenatal diagnostics and induction of labor is subject to comprehensive counseling by multidisciplinary teams in HTCs.

Peripartum interventions including episiotomy and neuraxial techniques are important during delivery. The episiotomy rate in our cohort was lower than seen in the general population (20% vs 26%). In women with inherited bleeding disorders, episiotomy tended to be more often associated with severe primary PPH (15% vs 10%; $P = .15$). This advocates for careful use of episiotomy in this population. Lastly, the included population received neuraxial anesthesia significantly less often than the general Dutch population, suggesting hesitance by healthcare workers to provide, or by women with bleeding disorders to undergo, this type of labor anesthesia to women with bleeding disorders.

Our national cohort is unique as it covers all Dutch HTCs and was realized through an extensive search to ensure a large, representative dataset. Through comparison with the general population by using the Dutch Perinatal registry, we were able to compare these populations during the same time frame. Limitations of this study are linked to the exclusion of deliveries outside the HTCs (though this rarely occurs when women require peripartum clotting factor concentrates or when a fetus might be affected), the retrospective nature of this study, and the incomplete national Perinatal registry regarding all potential PPH risk factors. In addition, Perined also includes the study population of this paper and VWD remains underdiagnosed, which hampers true comparison with a nonbleeding disorder population [28]. Lastly, unfortunately in this study data on secondary PPH are lacking while secondary PPH can occur in both women with VWD and HC since their VWF and FVIII levels return to baseline in the days to weeks after delivery [15,18].

While the severe primary PPH incidence in HC and VWD is not clearly higher compared with the general population, there is certainly room for improvement in both women with bleeding disorders and the general population with probably undiagnosed bleeding disorder cases. Women who currently do not receive prophylactic treatment with clotting factor concentrate (ie, those with third-trimester clotting factor activity levels ≥50 IU/dL) might also benefit from prophylactic treatment to decrease the primary PPH incidence. Specific interventions might be warranted according to the specific subtypes of VWD since the PPH rate in especially type 2(B) VWD seems to stand out (Table 2). An international initiative to reach consensus on the optimal pregnancy management for VWD type 2B is currently running [29]. In case of PPH the use of tranexamic acid, desmopressin, and clotting factor concentrates may be improved.

Meanwhile, the considerable proportion of women who received prophylaxis despite third-trimester clotting factor activity levels ≥50 IU/dL is apparent. Further studies should investigate whether increasing the cutoff level for prophylactic treatment with clotting factor concentrate and an increased trough level after treatment can reduce the severe primary PPH risk. Furthermore, additional data on the effect of opting out of prenatal diagnostics, induction of labor, neuraxial anesthesia, delivery location (non-HTC vs HTC), and patient-reported outcomes are warranted to improve counseling and care provision.

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AUTHOR CONTRIBUTIONS

M.P. and K.v.G. designed the study. M.P. and F.v.L. collected the data. M.P., K.v.G., T.L., and K.B. ran the first analyses. M.P. prepared the first draft of the article, which was revised by J.S., M.D., S.H., W.v.S., K.B., R.S., T.L., S.S., M.K., and K.v.G.

RELATIONSHIP DISCLOSURE

M.P., F.v.L., J.S., K.B., M.D., S.H., F.H.-M., T.L., A.M., L.N., W.v.S., R.S.: none. M.C.: participation in industry-sponsored studies by Bayer, CSL Behring, Novo Nordisk, and Roche and consultancy fees from Sobi, CSL Behring, and Novo Nordisk. S.S.: unrestricted research grant from Bayer. J.E.: received research grant from CSL Behring. M.K.: received unrestricted research grants from Sobi, in the past (payments to the

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SUPPLEMENTARY MATERIAL

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