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ORIGINAL ARTICLE

High prevalence of postpartum hemorrhage in women with rare bleeding disorders in the Netherlands: retrospective data from the RBiN study

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Abstract

Background: Women with rare bleeding disorders (RBDs), including coagulation factor deficiencies and fibrinolytic disorders, may have a higher risk of postpartum hemorrhage (PPH). Information on this patient category is lacking in the existing PPH guidelines because data on PPH in patients with RBDs are scarce.

Objective: To describe the prevalence of PPH in women with an RBD and evaluate the use of peripartum hemostatic prophylaxis.

Methods: In the Rare Bleeding Disorders in the Netherlands (RBiN) study, patients with RBDs (n = 263) were included from all 6 Dutch hemophilia treatment centers. Patient–reported information on delivery, peripartum hemostatic prophylaxis, and occurrence of PPH was collected retrospectively. If available, information about the precise volume of postpartum blood loss was extracted from electronic patient files. PPH was defined as blood loss ≥500 mL (World Health Organization guideline).

Results: A total of 244 pregnancies, including 193 livebirths, were reported by 85 women. A considerable proportion of these women experienced PPH, ranging from 30% in factor V deficiency to 100% in hyperfibrinolysis. Overall, PPH was reported in 44% of deliveries performed with and 53% of deliveries performed without administration of peripartum hemostatic prophylaxis. Blood loss was significantly higher in deliveries without administration of hemostatic prophylaxis (median 1000 mL) compared to deliveries with administration of prophylaxis (median 400 mL) (p = 0.011). Patients with relatively mild deficiencies also frequently experienced PPH when peripartum hemostatic prophylaxis was omitted.

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A complete list of the members of the RBiN Study Group appears in Appendix.

Conclusion: PPH is common in rare coagulation factor deficiencies, both severe and mild, and fibrinolytic disorders, especially when peripartum prophylactic hemostatic treatment was not administered. The use of prophylactic hemostatic treatment was associated with less postpartum blood loss.

KEYWORDS
blood coagulation disorders, delivery, obstetric, fibrinolysis, postpartum hemorrhage, pregnancy

1 | INTRODUCTION

Rare bleeding disorders (RBDs) refer to congenital deficiencies of fibrinogen, factor (F) II, FV, FV + FVIII, FVII, FX, FXI, and FXIII, and to disorders of fibrinolysis. Overall, typical symptoms of all RBDs are bleeding of the mucosal tract and profound bleeding during and after invasive procedures and during delivery. However, the clinical presentation of patients with RBDs is heterogeneous, varying from no or only minor bleeding to life-threatening bleeding [1–3]. Bleeding phenotype not only varies considerably between patients with different RBDs but also varies between patients with similar RBDs and comparable residual coagulation factor activity levels. Previous data from the Rare Bleeding Disorders in the Netherlands (RBiN) study showed strong correlations between baseline coagulation factor activity levels and the International Society on Thrombosis and Haemostasis-bleeding assessment tool (ISTH-BAT) scores for FII and FX deficiencies, but only moderate correlations for deficiencies of fibrinogen, FV, FVII, FXIII, and α2-antiplasmin (α2-AP) and no correlation for FXI deficiency [4]. Corresponding results were reported in the European Network of Rare Bleeding Disorders (EN-RBD), in which strong associations for deficiencies of fibrinogen, FV + FVIII, FX, and FXIII, a poor association for FV and FVII deficiency, and no association for FXI deficiency were found [5].

In the general Dutch population, the incidence of postpartum hemorrhage (PPH) is 19% and that of severe PPH is 6.4% [6,7], although these percentages may differ between studies according to the PPH definition that is used. In normal pregnancies, a physiological hypercoagulable state develops due to decreasing levels of anticoagulant factors and increasing plasma levels of most coagulation factors. More specifically, during pregnancy coagulation factor activity levels of fibrinogen, FVII, and FX normally increase, FII and FV levels do not change or only slightly increase, and FXIII levels decrease. Reports on FXI activity levels are contradictory [8,9].

For women with an RBD, including those with a mild coagulation factor deficiency and/or a mild bleeding phenotype, pregnancy and delivery are often major hemostatic challenges [8,10]. However, little is known about the actual bleeding risk during delivery in this patient group because of the rarity of RBDs [10]. Currently, no studies have identified factor activity levels that have a risk of peri- and postpartum bleeding similar to that in the general population. Moreover, real-life data per RBD on peri- and postpartum bleeding are scarce. For most women with an RBD, the specific coagulation factor will remain low without treatment, leading to persistent bleeding risk during pregnancy. This subsequently leads to a high risk of PPH, particularly in severe cases of an RBD [8,10,11].

Essentials

- Data on postpartum hemorrhage in women with rare bleeding disorders are scarce.
- A high prevalence of postpartum hemorrhage was found in rare coagulation factor deficiencies and fibrinolytic disorders.
- Postpartum hemorrhage was frequently observed in both severe and mild coagulation factor deficiencies and fibrinolytic disorders when prophylactic peripartum hemostatic treatment was not administered.
- Patients who received prophylactic peripartum hemostatic treatment experienced less postpartum blood loss.

Recently, bleeding risk and management of (non-)symptomatic hemophilia carriers during pregnancy and delivery have received much attention. The observed high postpartum bleeding rate, even if coagulation factor activity levels were normalized, resulted in an updated Dutch guideline in which higher target factor activity levels at delivery are recommended in hemophilia carriers [12]. By contrast, little research has been conducted in women with an RBD. Insights from both patient groups will ultimately lead to improved and individualized care during pregnancy and delivery in women with an RBD, most likely resulting in a reduced PPH rate.

The aim of this RBiN substudy is to describe the prevalence of PPH in Dutch women with an RBD and to evaluate the use of prophylactic peripartum hemostatic treatment in relation to the occurrence of bleeding complications.

2 | PATIENTS AND METHODS

2.1 | Study design

The RBiN study is a nationwide cross-sectional study among patients from all 6 Dutch hemophilia treatment centers with a diagnosis of a congenital

RBD, including coagulation factor deficiencies and disorders of fibrinolysis [4]. Patients were included from October 1, 2017 to November 30, 2019. For all patients, RBD diagnosis was established after referral to a hemophilia treatment center because of hemorrhagic diathesis, family history, and/or abnormalities in screening laboratory tests. Patients were eligible if they were one year or older. The design of the RBiN study, including specific patient inclusion criteria, has been previously published [4]. Hyperfibrinolysis was defined as a euglobulin clot lysis time ratio before and after application of a tourniquet ≥5.8 (reference range 1.2-5.7, locally validated assay). Plasminogen activator inhibitor type 1 (PAI-1) deficiency was defined as PAI-1 activity level below the detection limit and PAI-1 antigen level below the lower limit of normal (reference range, 3.4-39 ng/mL). All patients with hyperfibrinolysis or PAI-1 deficiency had normal α2-AP levels [4,13]. The study was approved by the Medical Ethical Committee of Arnhem-Nijmegen. All patients, and/or parents in case of minors, gave written informed consent.

2.2 | Assessment methods

2.2.1 | Patient–reported data

Participants were invited for a study visit to their hemophilia treatment center during which they were interviewed by the same investigator (JS) about their bleeding symptoms. The following 2 bleeding assessment tools (BATs) were used: the ISTH-BAT and a specific BAT for RBD patients (RBD-BAT) [14]. These BATs contain questions on the occurrence, timing, possible consequences (eg, anemia), and treatment of PPH. Primary PPH refers to excessive blood loss within 24 hours after birth, and secondary PPH to excessive blood loss after 24 hours to 6 weeks after delivery [15]. Consultation was defined as a clinical evaluation and/or detailed laboratory investigation or referral to a specialist. Medical attention was used as a collective term to refer to all types of PPH treatment that are included in the ISTH-BAT and the RBD-BAT (ie, consultation only/oxytocin intravenous infusion, additional uterotonic medication, iron therapy, antifibrinolytic therapy, desmopressin, plasma, thrombocyte transfusion, factor concentrate, red blood cell transfusion, any procedure requiring examination under anesthesia, uterine balloon/package to tamponade the uterus, and any procedure requiring critical care or surgical intervention). The different types of PPH treatment were categorized as supportive treatment (iron therapy or red blood cell transfusion), obstetric measures, and hemostatic agents.

Furthermore, a specific record was created for each individual delivery, including detailed patient–reported information about location, mode, and gestational age at the time of delivery, use of pain medication, prophylactic hemostatic treatment during labor, and child outcome. Prophylactic peripartum hemostatic treatment included all types of hemostatic products that were used during labor to prevent PPH, ie, tranexamic acid, desmopressin, thrombocyte transfusion, plasma, or a specific factor concentrate. A stillbirth referred to the delivery of a newborn who died before or during birth at or after 24 weeks of gestation. A miscarriage was defined as a spontaneous loss of pregnancy before 24 weeks of gestation [16].

Finally, all women were asked to complete an extensive self-administered questionnaire that included questions about their bleeding disorder, social aspects, and quality of life. This questionnaire also contained a specific section about pregnancy and delivery.

2.2.2 | Quantification of postpartum blood loss by healthcare professionals

For each participant, electronic patient files were searched for detailed delivery information.

If available, information about the precise volume of postpartum blood loss, quantified by a healthcare professional, was extracted.

2.2.3 | Laboratory phenotype

During the study visit, blood samples were taken for laboratory testing. Coagulation factor activity levels were then measured at baseline in a central laboratory (Radboud University Medical Center) to exclude bias due to interlaboratory differences. PAI-1 activity and antigen levels were the lowest levels ever recorded because of diurnal variations. In patients with hyperfibrinolysis, the euglobulin clot lysis time ratio was measured during the diagnostic work-up at the outpatient clinic and was not repeated in the RBiN study.

2.3 | Definition of PPH

The precise volume of postpartum blood loss was preferably used to determine whether a delivery was complicated by PPH. PPH was defined as blood loss ≥500 mL after birth and severe PPH as blood loss ≥1000 mL [15,17]. If the volume of blood loss was not documented in patient files, the occurrence of PPH was deduced from the patient's answers to questions from the BATs about the total number of deliveries, frequency of PPH, and the number of deliveries requiring treatment for PPH. In case of a discrepancy between the documented volume of blood loss and patient–reported information about the occurrence of PPH, data from electronic patient files were used. Deliveries in which the exact amount of blood loss was documented were also analyzed separately.

2.4 | Timing of delivery in relation to RBD diagnosis

In deliveries before RBD diagnosis, physicians have no indication to start prophylactic peripartum hemostatic treatment. These deliveries might be a patient's first bleeding manifestation. Therefore, a separate subanalysis of deliveries before and after RBD diagnosis was performed.

The age at RBD diagnosis was extracted from the electronic patient file for each woman. The maternal age at delivery was established in different ways (Supplementary Figure S1). In most women, the maternal age at delivery was extracted from the self-administered

questionnaire and was thus patient–reported. For women who did not complete the questionnaire, electronic patient files were searched for maternal age at delivery. "Deliveries before RBD diagnosis" were defined as deliveries in which the maternal age at delivery was lower than the age at RBD diagnosis. "Deliveries after RBD diagnosis" were defined as deliveries in which the maternal age at delivery was higher than the age at RBD diagnosis. Few women did not complete the questionnaire, and their electronic patient files did not include their maternal age at delivery. When their RBD was diagnosed in childhood or after reproductive years, their deliveries were classified as "deliveries after RBD diagnosis" and "deliveries before RBD diagnosis," respectively. When their RBD was diagnosed in the reproductive years, the timing of delivery in relation to RBD diagnosis could not be established, and these deliveries were excluded from the subanalysis. Moreover, deliveries in women whose age at RBD diagnosis was unknown or similar to maternal age at one of their deliveries were excluded from the subanalysis.

2.5 | Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 25. Categorical variables were presented as counts and percentages. Proportions were compared using Fisher's exact or chi-squared tests. Continuous variables were reported as medians with interquartile range (IQR) or range. Median values were compared with Mann-Whitney *U* tests. All *p* values are two-sided. *p* values lower than 0.05 were considered statistically significant.

3 | RESULTS

Women from the RBiN study who were ever pregnant were included in the current analysis (n = 85, Figure 1). These women reported 244 pregnancies, including one pregnancy termination due to a chromosomal disorder of the fetus, 47 miscarriages, 193 livebirths, and 3 stillbirths. Miscarriage rates varying from 10% in α2-AP deficiency to 50% in FVII deficiency were observed. Multiple miscarriages were reported in patients with quantitative and qualitative fibrinogen deficiencies, and in patients with FV, FVII, and FXI deficiencies (Figure 2).

3.1 | Prevalence of PPH: patient–reported outcomes

3.1.1 | Prevalence of PPH in women

Overall, 56 of 85 women (66%) ever experienced a PPH. In each RBD, a considerable proportion of women reported a medical history of PPH, ranging from 30% in FV deficiency to 100% in hyperfibrinolysis (Figure 3). PPH was mostly primary (n = 35, 63%), although 8 patients (14%) reported a secondary PPH. Two patients (4%) experienced both primary and secondary PPH, and PPH timing was unknown in 11 patients (20%). Medical attention for PPH was required in 77% of patients, and a prolonged hospital stay or readmission in 57% of patients. Anemia after PPH was reported by 73% of patients. Finally, 49% of the women with multiple registered pregnancies had more than one episode of PPH at different deliveries.

3.1.2 | Prevalence of PPH in all deliveries

A total of 190 livebirths and 3 stillbirths were analyzed (Table 1). More than half of the deliveries took place in a local hospital, nearly one-third in a hemophilia treatment center, and 13% at home. Vaginal delivery was performed in 159 births (82%) and cesarean section in 34 births (18%) (Figure 1). PPH occurred in 42% of vaginal deliveries performed with prophylactic peripartum hemostatic treatment and in 54% of vaginal deliveries without prophylactic peripartum hemostatic treatment (not significant). In cesarean sections, PPH occurred in 50% of deliveries performed with prophylactic peripartum hemostatic treatment and in 45% of deliveries without prophylactic peripartum hemostatic treatment (not significant). The different types of prophylactic peripartum hemostatic agents that were used are summarized in Supplementary Table S1.

Data on gestational age at delivery and occurrence of PPH were available for 168 deliveries. These deliveries were divided into the following 3 categories: a gestational age of <37 weeks (n = 11), a gestational age of 37 to 41 weeks (n = 123), and a gestational age of ≥41 weeks (n = 34). The highest PPH rate was observed in deliveries at a gestational age of <37 weeks (73% in women with gestational age of <37 weeks, 47% in women with gestational age of 37 to 41 weeks, and 53% in women with gestational age of ≥41 weeks), although the absolute number of deliveries in this category was small. Differences in PPH rates between the gestational age categories were not statistically significant (p = 0.248).

To differentiate between older and more recent deliveries, we split the deliveries in the following 2 categories: deliveries that took place before 2010 ("older deliveries") and deliveries that took place in or after 2010 ("recent deliveries"). Of the 193 deliveries in our cohort, 102 were older deliveries, 31 were recent deliveries, and data were missing for 60 deliveries. PPH occurred in 46% of the older deliveries (n = 47) and 47% of the recent deliveries (n = 14) (p = 1.00). In a subanalysis of deliveries that were performed with prophylactic peripartum hemostatic treatment, 4 of 10 older deliveries (40%) and 3 of 14 recent deliveries (21%) were accompanied by PPH (p = 0.393).

Finally, 3 women had twin pregnancies. In none of these women, prophylactic peripartum hemostatic treatment was given. PPH occurred in 2 of these 3 deliveries.

3.1.3 | Prevalence of PPH in deliveries before and after RBD diagnosis

The timing of RBD diagnosis was known in 147 of 193 deliveries: 86 deliveries took place before RBD diagnosis (59%) and 61 deliveries

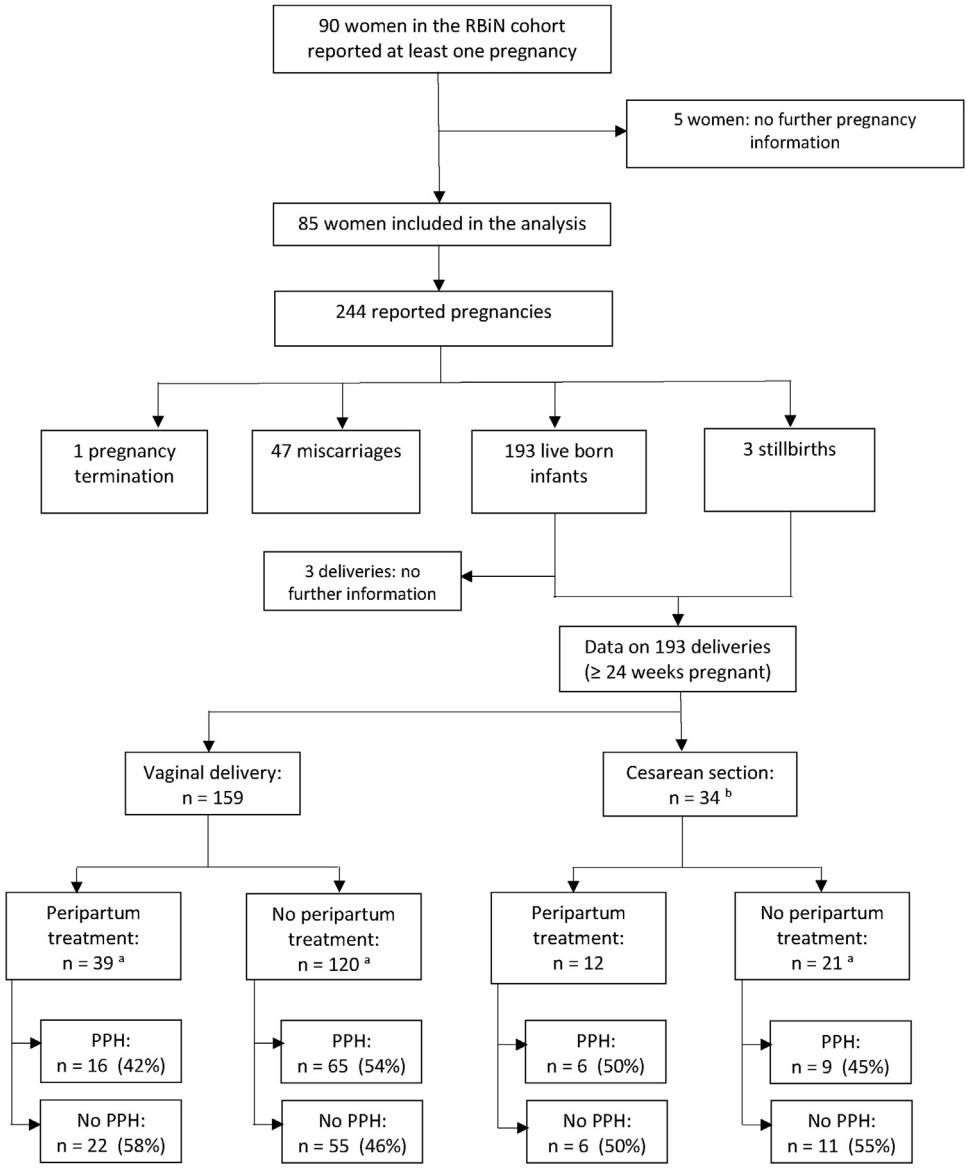

FIGURE 1 Flow chart. Peripartum treatment: all types of hemostatic products that were used during labor to prevent postpartum hemorrhage (PPH), ie, tranexamic acid, desmopressin, thrombocyte transfusion, plasma, or a specific factor concentrate. [a] Data on PPH missing for 1 delivery. [b] Data on prophylactic peripartum hemostatic treatment missing for 1 delivery.

occurred after RBD diagnosis (41%) (Supplementary Figure S2). Overall, PPH occurred in 56% of deliveries before RBD diagnosis (n = 48) and 44% of deliveries after RBD diagnosis (n = 27). Prophylactic peripartum hemostatic treatment was given more frequently in deliveries after RBD diagnosis compared to deliveries before RBD diagnosis (69% and 4%, respectively). Before RBD diagnosis, PPH occurred in 55% of deliveries performed without prophylactic peripartum hemostatic treatment (n = 46) and in 67% of deliveries performed with prophylactic peripartum hemostatic treatment (n = 2) (p = 1.00). After RBD diagnosis, PPH occurred in 37% of deliveries performed without prophylactic peripartum hemostatic treatment (n = 7) and in 48% of deliveries performed with prophylactic peripartum hemostatic treatment (n = 20) (p = 0.579).

3.1.4 | Prevalence of PPH in deliveries per RBD

An overview of PPH prevalence per RBD is provided in Figure 4 and Supplementary Table S2. In all coagulation factor deficiencies, a considerable proportion of deliveries performed without prophylactic peripartum hemostatic treatment was complicated by PPH, ranging from 17% in FV deficiency to 63% in FXI deficiency. PPH also occurred in patients with mildly reduced to near-normal activity levels of the deficient factor. Use of prophylactic peripartum hemostatic treatment was associated with a lower bleeding rate, most markedly in FVII deficiency. By contrast, in quantitative fibrinogen and FV deficiencies, a higher PPH prevalence was observed when prophylactic peripartum hemostatic treatment was used (50% without vs. 57%

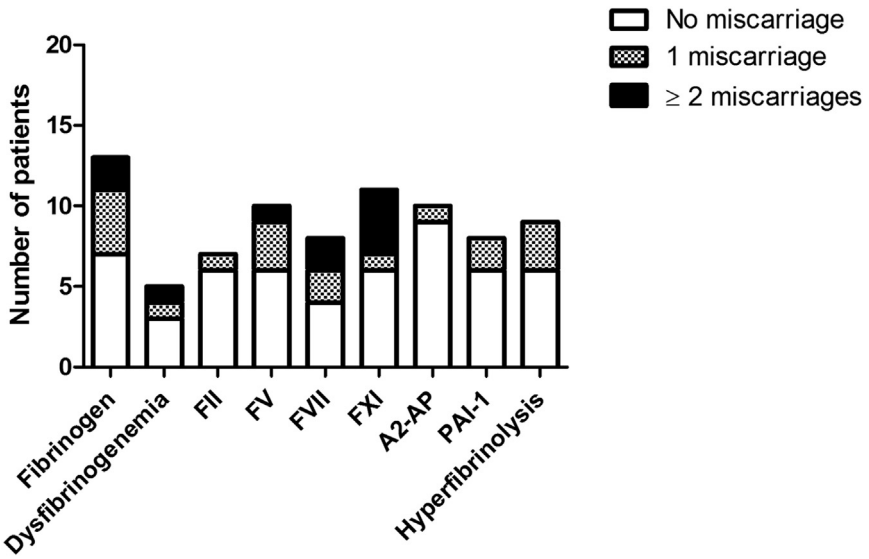

FIGURE 2 Number of reported miscarriages per patient, categorized per type of rare bleeding disorder (RBD). A2-AP, alpha 2-antiplasmin; PAI-1, plasminogen activator inhibitor type 1.

with prophylactic peripartum hemostatic treatment and 17% without vs. 43% with prophylactic peripartum hemostatic treatment, respectively, Supplementary Table S2). However, these deliveries were reported by patients with more severe deficiencies (Figure 4).

In patients with α2-AP deficiency, 5 deliveries (56%) were complicated by PPH when prophylactic peripartum hemostatic treatment was used, whereas only one-third of deliveries without prophylactic peripartum hemostatic treatment were associated with PPH (n = 4) (Figure 4F). Omission of prophylactic peripartum hemostatic treatment was associated with PPH in the majority of deliveries in patients with PAI-1 deficiency (62%). In patients with hyperfibrinolysis, most deliveries were accompanied by PPH, irrespective of the prophylactic peripartum use of hemostatic agents. Tranexamic acid, with or without desmopressin, was most frequently used as prophylactic treatment in these deliveries (Supplementary Table S1).

3.2 | Quantification of postpartum blood loss by healthcare professionals

The precise amount of postpartum blood loss was registered in 55 deliveries, including 46 vaginal births and 9 cesarean sections. Median volume of blood loss was 600 mL, with a range from 100 mL to 5000 mL (Supplementary Table S2). No significant differences were found between vaginal births (median 600 mL, range 100-5000 mL) and cesarean sections (median 600 mL, range 200-1800 mL) (p = 0.900). PPH was observed in 62% of deliveries, and severe PPH in 38% of deliveries. Overall, the amount of blood loss was heterogeneous but significantly higher in deliveries performed without prophylactic peripartum hemostatic treatment (median 1000 mL, IQR 500-2875 mL) compared to deliveries with prophylactic peripartum hemostatic treatment (median 400 mL, IQR 200-1200 mL) (p = 0.011, Figure 5). The heterogeneity in the amount of postpartum blood loss per RBD is shown in Supplementary Figures S3 and S4.

The precise amount of postpartum blood loss was quantified by healthcare professionals in 14 deliveries before RBD diagnosis and in 34 deliveries after RBD diagnosis. The median volume of postpartum blood loss before RBD diagnosis was 2500 mL (range 200-5000 mL) compared to 450 mL (range 100-2700 mL) after RBD diagnosis ($p < 0.001$).

3.3 | Obstetric causes

In few deliveries, obstetric causes were reported by patients as (partial) explanation for PPH (Supplementary Table S3, Supplementary Figures S3 and S4). Uterine atony was reported in 3 deliveries, a postpartum

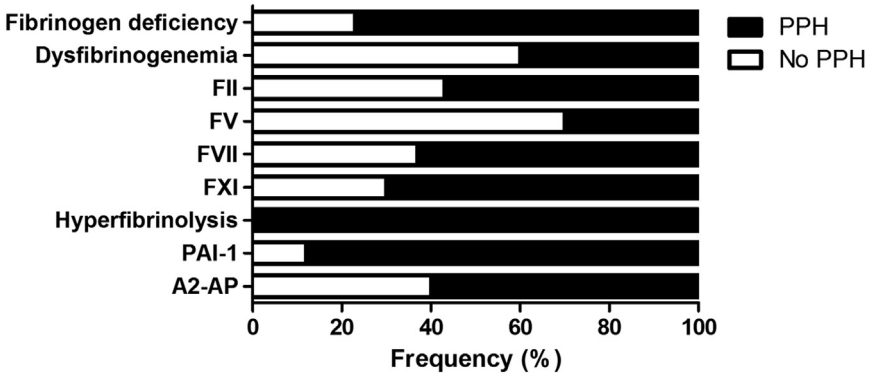

FIGURE 3 Proportion of patients with a medical history of postpartum hemorrhage, categorized per type of RBD. A2-AP, alpha 2-antiplasmin; PAI-1, plasminogen activator inhibitor type 1.

TABLE 1 Characteristics of reported deliveries

Number of deliveries at or after 24 weeks of gestation, *n*	193			
Livebirth, *n* (%)	190 (98.4)			
Stillbirth, *n* (%)	3 (1.6)			
Gestational age at birth in weeks, median (range) [a]	40 (24-42)			
Type of rare bleeding disorder	**Number of deliveries, *n* (%)**	**Number of women, *n* (%)**	**Coagulation factor activity level, median (range)**	**ISTH-BAT score, median (IQR)**
Fibrinogen deficiency (quantitative)	40 (20.8)	13 (15.3)	1090 mg/L (200-2730)	11 [f] (5-18)
Dysfibrinogenemia	8 (4.1)	5 (5.9)	1170 mg/L (780-2000)	7 [f] (5-13)
FII	17 (8.8)	7 (8.2)	58% (47-68)	4 [f] (2-9)
FV	19 (9.8)	10 (11.8)	39% [d] (3-54)	17 (6-27)
FV + FVIII	1 (0.5)	1 (1.2)	FV 93%, FVIII 88% [e]	6 (NA)
FVII	18 (9.3)	8 (9.4)	24% (1-78)	11 [f] (9-15)
FX	3 (1.6)	2 (2.4)	27-50% [e]	- [g]
FXI	33 (17.1)	11 (12.9)	36% (2-57)	9 (5-14)
FV Amsterdam	1 (0.5)	1 (1.2)	344% [e]	16 (NA)
α2-AP	21 (10.9)	10 (11.8)	71% (23-76)	10 [h] (4-21)
PAI-1	15 (7.8)	8 (9.4)	Act: <1.0 (<1.0 to <1.0) Ag: <2.5 (<2.5 to 3.2)	12 [h] (10-19)
Hyperfibrinolysis	17 (8.8)	9 (10.6)	8.1 (5.8-10.6)	13 (10-16)
Mode of delivery, n (%)				
Vaginal	159 (82.4)			
Cesarean section	34 (17.6)			
Place of delivery, n (%) [b]				
Local hospital	103 (53.6)			
Hemophilia treatment center	60 (31.3)			
Home	25 (13.0)			
Birth hotel	4 (2.1)			
Pain medication, n (%) [c]				
None	115 (62.2)			
Epidural or spinal anesthesia	29 (15.7)			
General anesthesia	16 (8.6)			
Other (e.g. oral, subcutaneous, intramuscular, intravenous)	25 (13.5)			

Coagulation factor activity level and International Society on Thrombosis and Haemostasis-bleeding assessment tool (ISTH-BAT) score are reported per included woman. For FV Amsterdam, the reported value in the column for coagulation factor activity level is the TFPI level (anti–K1). For patients with hyperfibrinolysis, the reported value in the column for coagulation factor activity level is the euglobulin clot lysis time ratio.

α2-AP, alpha 2-antiplasmin; Act, activity; Ag, antigen; NA, not applicable; PAI-1, plasminogen activator inhibitor type 1.

[a] Data missing for 3 deliveries.

[b] Data missing for 1 delivery.

[c] Data missing for 8 deliveries.

[d] Laboratory data missing for 1 woman.

[e] Absolute values were represented for each woman because of the low number of included women for this RBD.

[f] ISTH-BAT score missing for 1 woman.

[g] ISTH-BAT score missing for both women with FX deficiency.

[h] ISTH-BAT score missing for 3 women.

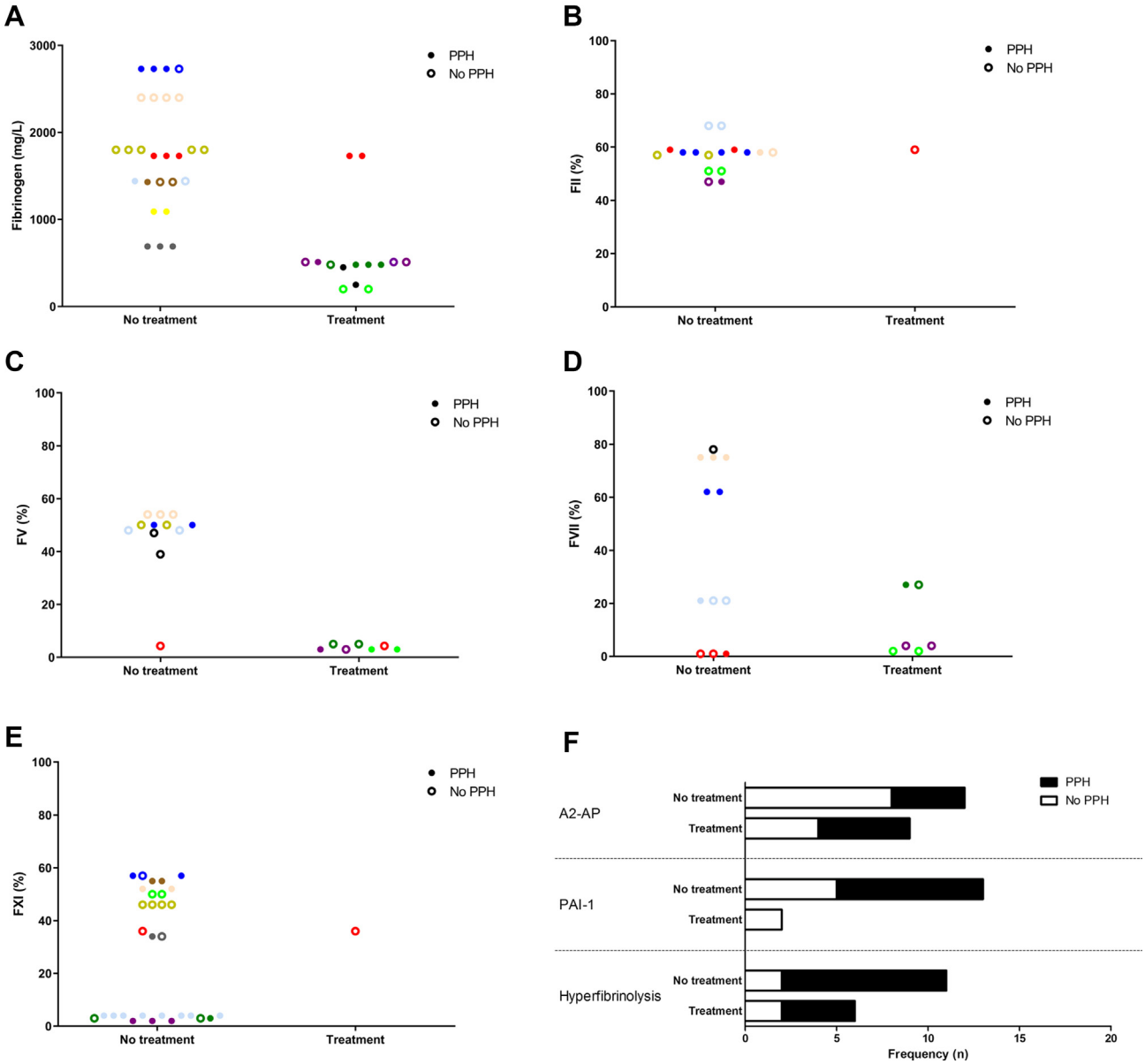

FIGURE 4 Association between type of RBD, use of prophylactic peripartum hemostatic treatment, and prevalence of postpartum hemorrhage. Panel A shows deliveries in patients with a quantitative fibrinogen deficiency, panel B shows deliveries in patients with FII deficiency, panel C shows deliveries in patients with FV deficiency, panel D shows deliveries in patients with FVII deficiency, panel E shows deliveries in patients with FXI deficiency, and panel F shows deliveries in patients with a fibrinolytic disorder. Each dot represents 1 delivery. In panels A-E, all deliveries reported by the same woman are represented in the same color (open and closed dots), and women who reported only 1 delivery are represented by the color black. A2-AP, alpha 2-antiplasmin; PAI-1, plasminogen activator inhibitor type 1.

curettage in 8 deliveries, episiotomy in 1 delivery, a subtotal rupture of the perineum in 1 delivery, placental problems in 3 deliveries, suspected preeclampsia in 1 delivery, and HELLP syndrome in 1 delivery. A combination of uterine atony and postpartum curettage and a combination of uterine atony and episiotomy were each described in 1 delivery.

3.4 | Treatment for PPH per woman

Forty-three patients reported that they required medical attention for their PPH. Of these 43 women, 19 women delivered before RBD diagnosis, 11 women delivered after RBD diagnosis, and the timing of RBD diagnosis was unknown in 13 patients. An overview of the different types of PPH treatment they received, categorized as supportive therapy, obstetric measures, and hemostatic agents, is provided in Table 2 for women who delivered before RBD diagnosis and in Table 3 for women who delivered after RBD diagnosis. Before RBD diagnosis, most common treatment types were supportive. After RBD diagnosis, supportive treatment was still frequently used, but treatment also shifted toward the use of hemostatic agents.

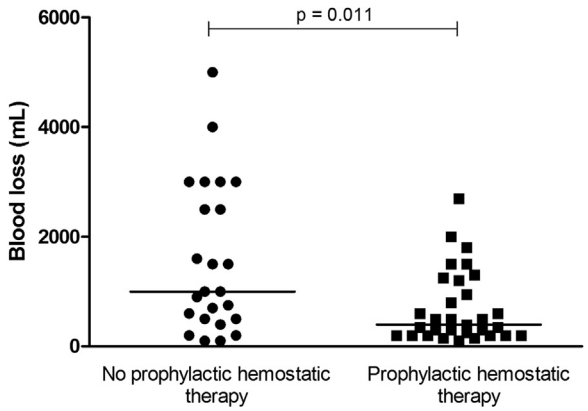

FIGURE 5 Amount of blood loss (mL) in deliveries performed without and with prophylactic peripartum hemostatic treatment.

4 | DISCUSSION

In the RBiN study, we demonstrated a high prevalence of PPH (66%) in patients with RBDs, including coagulation factor deficiencies and fibrinolytic disorders. Omission of prophylactic peripartum hemostatic treatment was not only frequently associated with PPH in patients with severe deficiencies but also in patients with mildly reduced to near-normal levels of the deficient coagulation factor. Importantly, a lower amount of blood loss was observed when prophylactic peripartum hemostatic agents were used.

PPH prevalence in this RBiN substudy was high compared to studies among patients with other inherited bleeding disorders. In a large combined Dutch cohort study including patients with von Willebrand disease (VWD), congenital platelet defects, and RBDs from 3 nationwide cross-sectional studies, 50% of all women who underwent labor experienced a PPH [18]. In a Dutch and an American cohort of women with VWD, PPH was self–reported by 51% and 59%, respectively [19,20], and in a group of 74 parous women with low von Willebrand factor levels (30-50 IU/dL) and a personal bleeding history, 63.5% self–reported PPH [21]. Only women with congenital platelet defects reported PPH more frequently (74%-78%) [22,23]. As studies using self–reported data are at risk of recall bias, we conducted a subgroup analysis of deliveries in which blood loss was quantified by healthcare professionals. In these 55 deliveries, the prevalence of PPH was 62% with a majority of these bleedings classified as severe. In studies on VWD and hemophilia using objective data from patient files as measure of blood loss, lower prevalences of primary PPH were described, varying from 19% to 44% [20,24–30]. A recent systematic review demonstrated a PPH rate ranging from 20% (using cohort data) to 63% (using individual-patient data) in hemophilia carriers [31].

However, studies reporting on the prevalence of PPH per RBD are difficult to compare because there is large heterogeneity in the methods of measuring PPH and the use of prophylactic peripartum hemostatic treatment. Moreover, multiple definitions of PPH, comprising different blood loss cutoff values, are used worldwide. Finally, in the majority of cases, PPH is caused by obstetric complications such as uterine atony, obstetric lacerations, and retained placental tissue. Coagulation factor deficiencies only account for <1% of PPH [32]. Missing information about possible obstetric causes or other risk factors for PPH further complicates the comparison of studies. In our cohort, obstetric problems were reported in only 20 deliveries (10%), although this is probably an underestimation because of the use of patient–reported data.

In our cohort, PPH was mostly observed in deliveries performed without prophylactic peripartum hemostatic treatment. In some RBDs, however, higher bleeding rates were observed when prophylactic peripartum hemostatic treatment was used, although these subgroups were small. This contradiction has been found earlier in studies on VWD and hemophilia in which an increased PPH risk was observed in deliveries performed with prophylactic treatment compared to deliveries without prophylactic treatment [24,25,33]. A potential explanation is that patients who are selected for prophylactic peripartum hemostatic treatment have a more severe coagulation factor deficiency or an increased bleeding tendency compared with untreated diagnosed patients and that the increase in factor activity levels with hemostatic prophylaxis is insufficient. A minority of patients received a more general prophylactic peripartum hemostatic treatment (with tranexamic acid or desmopressin) instead of treatment products targeted at their specific RBD. Another important parameter is the timing of hemostatic therapy. For each pregnant woman with an RBD, a personalized peripartum treatment plan is made that includes recommendations on when to initiate hemostatic therapy (eg, at start of contractions). However, when the interval between treatment and delivery is extremely short or extremely long due to an unexpectedly rapid or prolonged labor, plasma levels can be low and hemostasis at delivery remains insufficient. Unfortunately, information about the exact timing of prophylactic peripartum hemostatic treatment in our cohort is lacking. Nevertheless, the median amount of blood loss in our RBD cohort was significantly higher in deliveries without prophylaxis (1000 mL) than in deliveries with prophylaxis (400 mL).

Interestingly, a substantial number of deliveries performed without prophylactic peripartum hemostatic treatment in patients with mildly reduced to near-normal baseline coagulation factor activity levels were complicated by PPH in our study population. These observations are consistent with previous data from the RBiN study, in which only moderate correlations between factor activity levels and bleeding severity were found for deficiencies of fibrinogen, FV, and FVII, and no correlation for FXI deficiency [4]. Another possible explanation is that absolute coagulation factor activity levels at delivery in women with mild deficiencies are still low compared with the physiologically increased factor activity levels that are achieved in normal pregnancies. The fact that near-normal baseline factor activity levels might not be enough to guarantee adequate hemostasis during delivery should be taken into account when determining whether prophylactic therapy should be used. Prospective studies on larger cohorts of patients with RBDs are required to search for novel cutoff values that reliably predict postpartum bleeding risk.

In the general population, 10.8% of women will experience 1 miscarriage in their lifetime, 1.9% of women 2 miscarriages, and 0.7% of women 3 or more miscarriages [34]. In our RBiN substudy, a higher

TABLE 2 Specifications of PPH treatment in women who delivered before RBD diagnosis and required medical attention for their PPH

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Supportive treatment																			
Iron therapy	■	■	■	■	■		■	■		■	■	■	■	■	■			■	■
Red blood cell transfusion		■			■			■	■	■	■			■		■		■	
Obstetric measures																			
Consultation only or intravenous oxytocin infusion																			
Additional uterotonic medication			■									■	■					■	
Any procedure requiring examination under anesthesia								■					■						
Uterine balloon or package to tamponade the uterus																	■		
Any procedure requiring critical care or surgical intervention (includes internal iliac artery legation, uterine artery embolization, uterine brace sutures)										■									
Hemostatic agents																			
Tranexamic acid																			
Desmopressin																			
Plasma						■													
Thrombocyte transfusion																			
Factor concentrate																	■		
Number of deliveries that required a type of PPH treatment	1	2	3	1	1	1	1	2	1	2	1	2	2	2	1	1	1	8	1

In total, 56 women ever experienced a PPH. Forty-three of these women required medical attention for their PPH. The medical attention that the 19 women who delivered before RBD diagnosis received is represented in this table. Each column represents a single woman. A red color indicates that a woman ever received that specific type of PPH treatment.

TABLE 3 Specifications of PPH treatment in women who delivered after RBD diagnosis and required medical attention for their PPH

Patients	1	2	3	4	5	6	7	8	9	10	11
Supportive treatment											
Iron therapy											
Red blood cell transfusion											
Obstetric measures											
Consultation only or intravenous oxytocin infusion											
Additional uterotonic medication											
Any procedure requiring examination under anesthesia											
Uterine balloon or package to tamponade the uterus											
Any procedure requiring critical care or surgical intervention (includes internal iliac artery legation, uterine artery embolization, uterine brace sutures)											
Hemostatic agents											
Tranexamic acid											
Desmopressin											
Plasma											
Thrombocyte transfusion											
Factor concentrate											
Number of deliveries that required a type of PPH treatment	1	1	2	- [a]	2	4	4	2	1	1	1

In total, 56 women ever experienced a PPH. Forty-three of these women required medical attention for their PPH. The medical attention that the 11 women who delivered after RBD diagnosis received is represented in this table. Each column represents a single woman. A red color indicates that a woman ever received that specific type of PPH treatment.

[a] Number of deliveries that required a type of PPH treatment is unknown.

miscarriage rate was observed in almost all coagulation factor deficiencies (40%-50%, except FII deficiency) and fibrinolytic disorders (25%-33%, except α2-AP deficiency). Previous research on hemophilia carriers reported slightly lower miscarriage rates, ranging from 12% to 31% [27,35–38]. Future studies are needed to elucidate the high miscarriage rate in patients with RBDs and to postulate possible preventive therapies.

4.1 | Study limitations

Data from the RBiN study are retrospectively collected, and most of the information about prophylactic peripartum hemostatic treatment and PPH is patient-reported. Dissimilarities in interviewing techniques or interpretation of patient–reported information were excluded because all patients were interviewed by the same investigator. However, a potential problem in studies using self–reported data is the risk of recall bias. This may result in an overestimation of the bleeding rate, because deliveries complicated by PPH are more likely to be remembered. By contrast, the bleeding rate may be underestimated because the guideline on PPH from the Dutch Society of Obstetrics and Gynecology defines PPH as postpartum blood loss of more than 1000 mL instead of more than 500 mL according to the World Health Organization definition [17,39]. Objective information from electronic patient files about the exact amount of blood loss was only available for a minority of deliveries. In the subanalysis of these 55 deliveries, PPH prevalence was higher than that observed in the overall analysis including self–reported data. As medical records were not available for all deliveries, the patient–reported information about prophylactic peripartum hemostatic treatment could not be verified for all cases, and data on obstetric risk factors for PPH were often lacking. Especially, the use of tranexamic acid may be underestimated because women may be unaware of the use of tranexamic acid during labor.

Moreover, PPH may be the first indication of a hemostatic defect, resulting in further analysis and eventually in an RBD diagnosis. Furthermore, women with a history of PPH may be more frequently treated with prophylactic hemostatic agents during subsequent deliveries. To reduce the risk of selection bias, we did not only include symptomatic RBD patients diagnosed because of a hemorrhagic diathesis but also heterozygous family members and patients who were diagnosed because of an abnormal preoperative coagulation screening.

Unfortunately, we had to use baseline factor activity levels because coagulation factor activity levels in the third trimester of pregnancy were unknown for most patients. However, as most coagulation factor activity levels increase or remain stable in pregnancies in healthy women, we expect that women in our cohort with mildly reduced to near-normal baseline factor activity levels also have a relatively mild deficiency in the third trimester. Furthermore, prepartum anemia is a risk factor for PPH, but we do not have information about the prepartum hemoglobin levels because the RBiN study was a cross-sectional study.

In the future, prospective studies on larger cohorts of patients with RBDs are required to obtain more data about pregnancy and delivery and to further investigate the association between place of delivery, coagulation factor activity levels, type and timing of prophylactic peripartum hemostatic treatment, and PPH. In these studies, prespecified and objective measures to quantify postpartum blood loss are a prerequisite. The prospectively collected data can be used to develop evidence–based guidelines and healthcare pathways for the management of pregnancy and delivery in patients with RBDs, aiming for a more uniform treatment and improved quality of care with a reduced PPH rate.

Meanwhile, physicians should be aware of the high PPH rate in women with RBDs. We advise women with a diagnosis of an RBD, especially if they are giving birth for the first time, to deliver in a hemophilia treatment center. In these specialized centers, hematologists, gynecologists, pediatricians, and specialist nurses work together in multidisciplinary teams to provide high-quality care by close monitoring of women during pregnancy and providing individualized peripartum treatment plans early. In the Netherlands, a new guideline on RBDs will be published soon, including recommendations on the use of prophylactic peripartum hemostatic treatment.

4.2 | Conclusion

In the RBiN study, a high prevalence of PPH was found in all RBDs, both in coagulation factor deficiencies and fibrinolytic disorders, and also in patients with mildly reduced to near-normal levels of the deficient coagulation factor. Less blood loss was seen in patients who received prophylactic hemostatic therapy during delivery. Prospective studies with pregnant RBD patients are needed to define adequate third trimester coagulation factor activity threshold levels and to collect more data on the optimal prophylactic peripartum hemostatic treatment.

AUTHOR CONTRIBUTIONS

K.M., M.H.C., R.E.G.S., M.P., L.N., P.L.d.E., I.C.K., W.L.v.H., and S.E.M.S. are members of the steering committee that designed the study and are delegates of all Dutch hemophilia treatment centers and patient society. N.M.A.B. is head of the Department of Hematology in the Radboud University Medical Center and head of the RBiN project management team. O.W.H.v.d.H. is a gynecologist in the Radboud University Medical Center with expertise in deliveries in patients with bleeding disorders. J.L.S. interviewed the patients; D.P.M.S.M.M. analyzed the data; D.P.M.S.M.M., L.N., and S.E.M.S. wrote the manuscript; and all authors revised the manuscript and gave final approval.

DECLARATION OF COMPETING INTERESTS

K.M. reports speaker fees from Bayer and Alexion, participation in trial steering committee for Bayer, consulting fees from Uniqure, and participation in data monitoring and endpoint adjudication committee for Octapharma. M.H.C. received investigator–initiated research and

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APPENDIX

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SUPPLEMENTARY MATERIAL

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