

University of Groningen

## Maternal and neonatal bleeding complications in relation to peripartum management in hemophilia carriers

Punt, M. C.; Waning, M. L.; Mauser-Bunschoten, E. P.; Kruip, M. J. H. A.; Eikenboom, J.; Nieuwenhuizen, L.; Makelburg, A. B. U.; Driessens, M. H. E.; Duvekot, J. J.; Peters, M.

*Published in:*  
Blood reviews

*DOI:*  
[10.1016/j.blre.2021.100826](https://doi.org/10.1016/j.blre.2021.100826)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2021

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

Punt, M. C., Waning, M. L., Mauser-Bunschoten, E. P., Kruip, M. J. H. A., Eikenboom, J., Nieuwenhuizen, L., Makelburg, A. B. U., Driessens, M. H. E., Duvekot, J. J., Peters, M., Middeldorp, J. M., Bloemenkamp, K. W. M., Schutgens, R. E. G., Lely, A. T., & van Galen, K. P. M. (2021). Maternal and neonatal bleeding complications in relation to peripartum management in hemophilia carriers: A systematic review. *Blood reviews*, 49, [100826]. <https://doi.org/10.1016/j.blre.2021.100826>

### **Copyright**

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### **Take-down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



## Review

# Maternal and neonatal bleeding complications in relation to peripartum management in hemophilia carriers: A systematic review

M.C. Punt<sup>a,\*</sup>, M.L. Waning<sup>a</sup>, E.P. Mauser-Bunschoten<sup>a</sup>, M.J.H.A. Kruip<sup>b</sup>, J. Eikenboom<sup>c</sup>, L. Nieuwenhuizen<sup>d</sup>, A.B.U. Makelburg<sup>e</sup>, M.H.E. Driessens<sup>f</sup>, J.J. Duvekot<sup>g</sup>, M. Peters<sup>h</sup>, J. M. Middeldorp<sup>i</sup>, K.W.M. Bloemenkamp<sup>j</sup>, R.E.G. Schutgens<sup>a</sup>, A.T. Lely<sup>j</sup>, K.P.M. van Galen<sup>a</sup>

<sup>a</sup> Van Crevelkliniek, University Medical Center Utrecht, University Utrecht, Heidelberglaan 100, 3584, CX, Utrecht, the Netherlands

<sup>b</sup> Department of Hematology, Erasmus University Medical Center, Doctor Molewaterplein 40, 3015, GD, Rotterdam, the Netherlands

<sup>c</sup> Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Center, Albinusdreef 2, 2333, ZA, Leiden, the Netherlands

<sup>d</sup> Department of Internal Medicine, Maxima Medical Center, Veldhoven, De Run 4600, 5504, DB, Veldhoven, the Netherlands

<sup>e</sup> Department of Hematology, University Medical Center Groningen, Hanzeplein 1, 9713, GZ, Groningen, the Netherlands

<sup>f</sup> Netherlands Hemophilia Patient Society, Stationsweg 6b, 3862, CG, Nijkerk, the Netherlands

<sup>g</sup> Department of Gynaecology and Obstetrics, Erasmus University Medical Center, Doctor Molewaterplein 40, 3015, GD, Rotterdam, the Netherlands

<sup>h</sup> Department of Pediatric Hematology, Emma Children's Hospital, University Medical Centers, location AMC, Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands

<sup>i</sup> Department of Obstetrics, Leiden University Medical Center, Albinusdreef 2, 2333, ZA, Leiden, the Netherlands

<sup>j</sup> Department of Gynaecology and Obstetrics, University Medical Center Utrecht, Heidelberglaan 100, 3584, CX, Utrecht, the Netherlands



## ARTICLE INFO

## Keywords:

Hemophilia  
Pregnancy  
Peripartum period  
Postpartum hemorrhage

## ABSTRACT

Currently, there is no consensus on the optimal management to prevent postpartum hemorrhage (PPH) in hemophilia carriers. We aimed to evaluate peripartum management strategies in relation to maternal and neonatal bleeding outcomes by performing an extensive database search up to August 2020. Seventeen case-reports/series and 11 cohort studies were identified of overall 'poor' quality describing 502 deliveries. The PPH incidence in the individual patient data was 63%; 44% for those women receiving prophylaxis to correct coagulation and 77% for those without (OR 0.23, CI 0.09–0.58) and in cohort data 20.3% (26.8% (11/41) vs. 19.4% (55/284) (OR: 1.53, 95% CI: 0.72–3.24), respectively. Peripartum management strategies mostly consisted of clotting factor concentrates, rarely of desmopressin or plasma. Tranexamic acid appears promising in preventing secondary PPH, but was not used consistently. Neonatal bleeding was described in 6 affected male neonates, mostly after instrumental delivery or emergency CS, but insufficient information was provided to reliably investigate neonatal outcome in relation to management. The high PPH risk seems apparent, at most mildly attenuated by prophylactic treatment. Prospective cohort studies are needed to determine the optimal perinatal management in hemophilia.

## 1. Introduction

Hemophilia is an X-linked congenital bleeding disorder with absent or decreased factor VIII (FVIII) in Hemophilia A (HA) and factor IX (FIX) in case of Hemophilia B (HB). The population prevalence of hemophilia is approximately 1:5000 males. [1] Women can be carriers of hemophilia. Due to lyonization of the unaffected X chromosome early in embryonic life, carriers can have lowered clotting factor levels <40 IU/dL and may need prophylactic treatment to prevent bleeding, including postpartum hemorrhage (PPH). [2–5] An increased risk of primary PPH with a prevalence of 20–51% has been reported, even with the current

standard of care. [6–9] This prevalence of PPH vastly exceeds the PPH prevalence seen in the general population of approximately 19%, and although the secondary PPH incidence remains unclear in this population, it is thought to exceed the <1% incidence seen in the general population as well. [10,11] PPH remains worldwide, the main cause of severe maternal morbidity and mortality. However, guidelines for peripartum management for hemophilia carriers are mainly based on an expert opinion level of evidence. [12]

In healthy pregnant women, a procoagulant state evolves to prepare for childbirth. This procoagulant state is the result of an increase in clotting factor levels and a decrease in anticoagulant factors. [13,14] In

\* Corresponding author at: P.O. Box 85500, 3508, GA, Utrecht, the Netherlands.

E-mail addresses: [m.c.punt-3@umcutrecht.nl](mailto:m.c.punt-3@umcutrecht.nl) (M.C. Punt), [K.P.M.vanGalen@umcutrecht.nl](mailto:K.P.M.vanGalen@umcutrecht.nl) (K.P.M. van Galen).

<https://doi.org/10.1016/j.blre.2021.100826>

Available online 20 March 2021

0268-960X/© 2021 The Authors.

Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

most carriers of HA, the FVIII level may increase two to threefold as in healthy pregnant women, however the absolute level is still less than in normal pregnancy, which leaves them at an increased risk of bleeding complications, both during childbirth and the postpartum period. [15,16] A minimal FIX increase is seen during pregnancy in healthy women and carriers of HB. [17,18] Clotting factor levels decline on postpartum day 3 and approach baseline pre-pregnancy levels after one week in hemophilia carriers, which increases the risk of secondary PPH compared to healthy women. [5,13,19]

Guidelines and expert papers concerning the management of delivery in carriers of hemophilia recommend timely preparation of an individualized delivery plan. [12,20–22] In carriers with preexisting low clotting factor level, clotting factor levels have to be monitored during the third trimester of pregnancy or before delivery. Potential prophylactic measures to prevent PPH consist of clotting factor concentrates or desmopressin (DDAVP), aiming at increasing the maternal clotting factor levels. In addition, the antifibrinolytic agent tranexamic acid can be administered to inhibit fibrinolysis. [16,23] Another key factor for a safe delivery depends on the (potentially) affected child. Neonates with severe hemophilia are at increased risk of intracranial hemorrhage (ICH), with an ICH incidence around 2.5%. [24–26] Delivery of a (potentially) affected neonate is a relative contraindication for invasive procedures such as fetal blood sampling and assisted vaginal deliveries, as vacuum extraction and forceps, since these interventions are associated with increased neonatal bleeding risk. [24]

In view of the increased risk of PPH for hemophilia carriers and the absence of an overview of the available evidence, the aim of this systematic review is to summarize all published obstetric and hematologic management strategies in hemophilia carriers and to investigate their relation to peripartum bleeding complications in both mother and child.

## 2. Methods

### 2.1. Protocol and registration

This systematic review was registered at PROSPERO (CRD42018091987) [27] and conducted according to PRISMA guidelines and Cochrane methodology. [28,29] This registration was combined with the systematic review on Von Willebrand Disease (VWD) [30] and follows the same methodology—yet during the data analysis phase, the decision was made to present the data in two separate papers due to size of the reported data and the difference in hemostatic defect. All observational (i.e. cohort, case-control, case series/reports) and intervention studies concerning peripartum management for obligate or proven carriers of hemophilia were eligible for inclusion. Only articles written in English, German, French or Dutch, containing original patient data published as full papers in peer reviewed journals, were included.

The review questions were:

1. Which third trimester and peripartum management strategies have been published?
2. What is the relation of these management strategies towards maternal and neonatal bleeding complications?

### 2.2. Search and study selection

The electronic search was conducted on November 1st of 2020 in the following databases: Pubmed/MEDLINE, The Cochrane Library, EMBASE and CINAHL (Supplement S1: Full search string all databases). No time or other limits were used. Both electronic and hard-copies were searched. The articles were independently screened by two authors (MCP and MW) and thereafter full-text screening was performed by two authors independently (MCP and KG). In case of disagreement at any stage of the selection process, a third author (KG) was consulted. Cross-referencing of the bibliography of the included studies was conducted to find any additional studies.

### 2.3. Data collection and risk of bias assessment

Data extraction was conducted by two independent authors (MCP and MW) using a standardized data extraction sheet (Supplement S2: Data extraction sheet). Primary PPH was defined as blood loss of 500 mL or more within 24 h, and secondary PPH as excessive blood loss needing medical attention from 24 h until three months after childbirth. Prophylactic treatment included correction of clotting factor levels and/or prophylactic tranexamic acid prescription. Management strategy included both prophylactic and PPH treatment. Study design was defined as cohort study in case all eligible patients during a certain time period were included into the study, and as case series if patient selection was not described. [31] Outcome measurements were noted as counts in case of individual data and as counts *and* percentages in cohort studies if available or possible to extract. The association between third trimester clotting factor levels and the incidence of PPH was evaluated by calculating the odds ratio (OR) with 95% confidence interval (CI) and by logistic regression analysis, and repeated with correction for prophylaxis. Each paragraph is divided into results from the individual patient data and results from cohort studies. The corresponding author was contacted in case of inaccessible full-texts or incomplete data.

Risk of bias was assessed for each study using the Chambers scale (Supplement S3: Chambers scale for quality assessment) and conducted by two independent authors (MCP and MW). The overall Chambers quality rating of studies is divided into 'good', 'satisfactory' or 'poor'. [32] Any disagreements were resolved by consulting a third author (KG).

## 3. Results

A total of 5971 articles were obtained after duplicate removal and inclusion of three additional papers found by cross-reference searching (Fig. 1). After title- and abstract screening, 423 articles were selected for full-text assessment. The final selection consisted of 17 case reports [33–49] and 11 cohort studies [17,18,50–58] describing a total of 502 deliveries (Table 1). The exact number of included hemophilia carriers was unclear due to incomplete reporting in one cohort study. [53] Individual patient data on 106 deliveries could be extracted from 17 case reports/series and six cohort studies (details available on request). Data on pregnancy management and outcome derived from the cohort studies are summarized in Table 2. [17,18,50–58].

### 3.1. Risk of bias

A summary of the quality assessment for all included studies according to sample size is provided in Table 3. Detailed quality assessment of each individual study is provided in Supplemental Table S4. The quality of the included studies was rated as 'poor' in 89% (25/28) of included papers, 'satisfactory' in two papers and 'good' in one paper.

#### 3.1.1. Prophylactic treatment strategies

In the individual patient data, information on hematologic prophylactic treatment could be extracted for 88 deliveries. Prophylactic treatment consisted mostly of FVIII concentrates, DDAVP and tranexamic acid for hemophilia A, and FIX concentrates or blood products (e.g. fresh frozen plasma) for hemophilia B carriers (Fig. 2). In all three deliveries where use of DDAVP was described, it was administered after cord clamping, without side effects. [42,53,59] One woman who was on continuous intravenous clotting factor correction with FVIII concentrates aiming at a target level FVIII 150–200 IU/dL developed a brachial deep vein thrombosis on postpartum day 10, after which FVIII infusions were stopped (no tranexamic acid administration reported). [48] Obstetric prophylactic management strategies were not mentioned, other than the use of oxytocin.

The cut off level for prophylactic treatment with clotting factor or DDAVP was mentioned in 43% (12/28) of the articles. This cut off level was set at 50 IU/dL of third trimester clotting factor levels in all 12

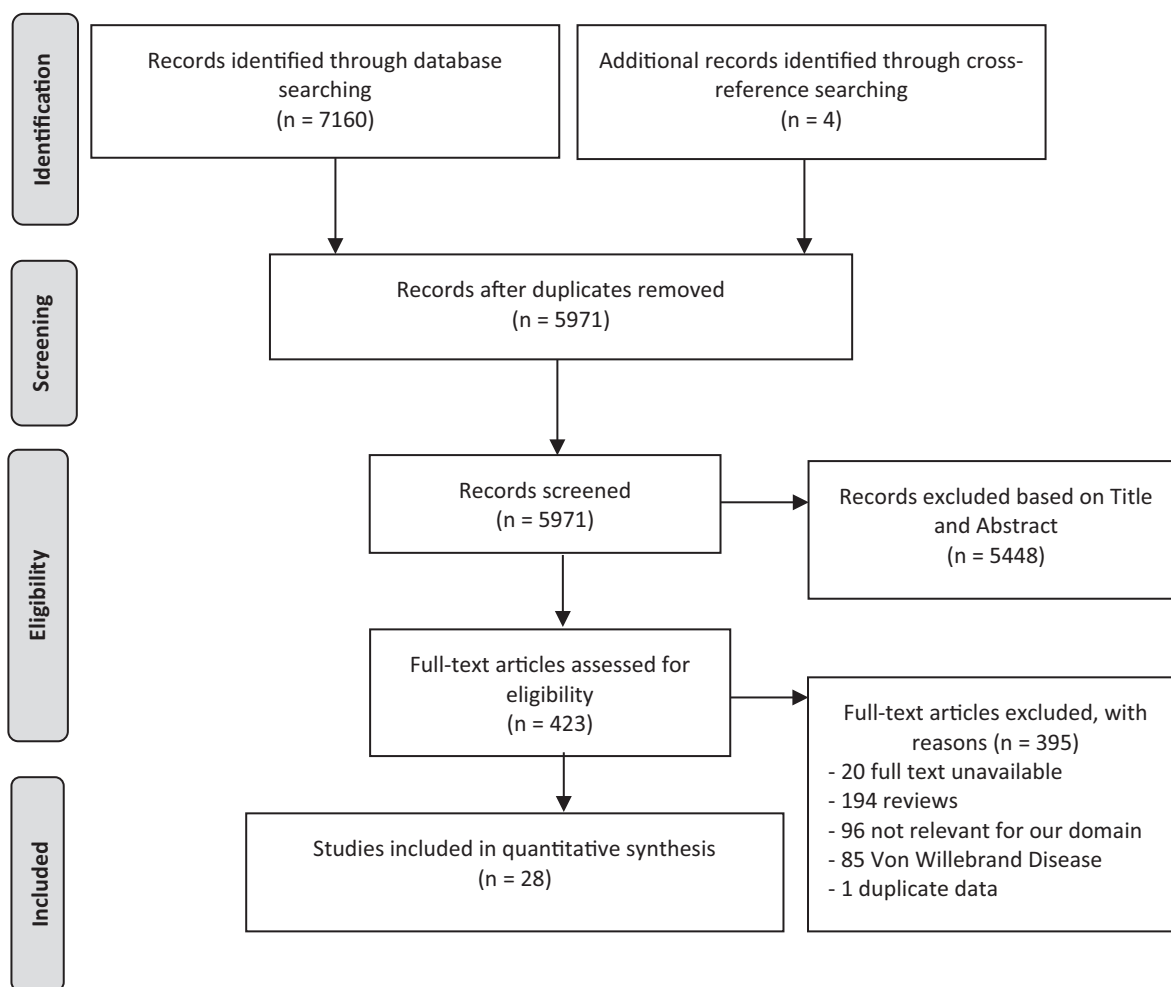


Fig. 1. Prisma Flowchart for identifying eligible studies on peripartum management of hemophilia carriers.

**Table 1**  
Number of published deliveries of hemophilia carriers per study type.

	Individual case descriptions	Cohort data	Total
	N	N	
Hemophilia			
Total	106	463	502 <sup>c</sup>
A	42	298	313 <sup>b</sup>
B	42	62	86
Unknown <sup>a</sup>	22	103	103

References: Cases hemophilia A [17,33,34,38,40–44,48,53,55,59], cohort hemophilia A [17,51,52,54,56], cases hemophilia B [17,35–37,39,42,46,47,49,51,53], cohort hemophilia, cases and cohort unknown hemophilia subtype [18,50,53].

<sup>a</sup> Unknown = Unknown subtype.

<sup>b</sup> The following women are mentioned as individual case descriptions and in cohort data: 22 hemophilia carriers [18,53], 18 hemophilia A carriers [17,53,55] and 18 hemophilia B carriers [17,51,53].

<sup>c</sup> Total deliveries: double entries omitted.

articles. [17,18,37–39,41–43,50,52,53,57]

In the cohort studies, hematologic prophylactic treatment strategies mostly consisted of clotting factor concentrates (6 of the 8 studies where prophylactic treatment was specified) (Table 2). Other replacement strategies consisted of fresh frozen plasma (2/8 studies), cryoprecipitate (1/8), DDAVP (1/8) or tranexamic acid (3/8). Information on obstetric prophylactic treatment was provided in one cohort study, namely the preemptive use of uterotonics. [58]

### 3.1.2. PPH in relation to prophylactic treatment

In the individual patient data, information on postpartum blood loss was available in 83% (88/106) of deliveries. PPH occurred in 63% (55/88) of these deliveries. In 87 deliveries, information on both peripartum blood loss and peripartum management was reported. In women who received prophylactic treatment to correct hemostasis, we found a lower PPH incidence compared to those who did not receive this (43.6% (17/39) vs. 77.1% (37/48); OR: 0.23, 95% CI: 0.09–0.58,  $p = 0.002$ ).

Mode of delivery (cesarean section) and nulliparity were most frequently reported as obstetric risk factors in 69% (60/87) and 54% (47/87) of deliveries, respectively. Both factors did not differ between the cases with and without PPH (cesarean sections: 69% (22/32 PPH) vs. 64% (18/28 no PPH) and nulliparity: 34% (10/29 PPH) vs. 39% (7/18 no PPH). PPH occurred as often in those women with 3rd trimester levels <50 IU/dL compared to those >50 IU/dL, despite prophylaxis (72.4% (21/29) vs. 88.0% (22/25); OR: 0.36, 95% CI: 0.08–1.53,  $p = 0.17$ ).

Six cohort studies reported on PPH occurrence in relation to prophylactic management strategies (Table 2). [17,50,56–58,60] Overall, no lower primary PPH incidence was seen in deliveries covered by prophylaxis compared to the deliveries without prophylaxis (26.8% (11/41) vs. 19.4% (55/284) (OR: 1.53, 95% CI: 0.72–3.24). One cohort study investigated the effect of tranexamic acid use vs. no prophylaxis on secondary PPH. This prophylactic treatment management strategy significantly lowered the secondary PPH incidence across the cohort of several bleeding disorders ( $P < 0.049$ ) without reported thrombotic complications. [52]

**Table 2**  
Summary of outcome data from cohort studies on hemophilia carriers.

Author, year	Number of included deliveries	Incidence PPH (% (N PPH/N total deliveries))	Management strategy (prophylactic, PPH treatment)
Nau, 2020 [50]	HA (N = 98) HB (N = 19)	HA - Primary PPH: 12% (12/98) - Secondary PPH: 11% (10/98) HB - Primary PPH: 26% (5/19) - Secondary PPH: 16% (3/19)	Prophylactic management in 29% (5/17) deliveries with primary PPH vs. 19% (19/100) without PPH. Prophylactic management consisted of desmopressin (N = 3), antifibrinolytics (N = 11), factor concentrate (N = 3) or factor concentrates + antifibrinolytics (N = 6).  PPH treatment consisted of blood transfusion for 3 carriers. No further information on PPH treatment strategies was provided.
Stoof, 2015 [17]	HA (N = 95) HB (N = 19)	HA - Prophylaxis: 50% (1/2) - No prophylaxis: 24% (22/93) HB - Prophylaxis: 75% (3/4) - No prophylaxis: 13% (2/15)	Prophylactic management consisted of clotting factor concentrates.  No information on PPH treatment strategies.
Zwagemaker, 2018 [56]	HA (N = 53) HB (N = 8)	HA - Prophylactic treatment: 100% (2/2) - No prophylactic treatment: 29% (15/51) HB - Prophylactic treatment: 0% (0/1) - No prophylactic treatment: 57% (4/7)	Prophylactic management consisted of clotting factor concentrates.  No information on PPH treatment strategies.
Chi, 2008 [18]	Hemophilia (N = 47)	Obligate and unknown hemophilia carriers: - Primary PPH: 19% (9/47)	Prophylactic management consisted of clotting factor concentrates.  PPH treatment consisted of blood transfusions for two cases. Other management strategies included oxytocin, tranexamic acid, or carboprost & oxytocin.
Kadir, 1997 [53]	Hemophilia (N = 46)	Suspected (N = 6)- and obligate (N = 24) carriers: - Primary PPH: 22% (10/46) - Secondary PPH: 11% (5/46)	Prophylactic management consisted of fresh frozen plasma, clotting factor concentrates or both.  PPH treatment consisted of blood transfusions, IV oxytocin, IV ergometrin or the oral contraceptive pill.

**Table 2 (continued)**

Author, year	Number of included deliveries	Incidence PPH (% (N PPH/N total deliveries))	Management strategy (prophylactic, PPH treatment)
Greer, 1991 [51]	HA (N = 34) HB (N = 9)	HA - Primary PPH: 0% (0/34) - Secondary PPH: 9% (3/34) HB - Prophylaxis: 0% (0/8) - No prophylaxis: 0% (0/1) - Secondary PPH: 11% (1/9)	Prophylactic management consisted of cryoprecipitate (HA) or fresh frozen plasma (HB).  PPH treatment for the 3 HA carriers consisted of uterine evacuation due to retained products of conception and blood transfusions (2 deliveries) and one woman was treated with cryoprecipitate, antibiotics and tranexamic acid (thought to be related to endometritis).
Lavin, 2020 [58]	Hemophilia (N = 25)	Low baseline clotting factor levels: - Primary PPH: 14% (1/7) - Secondary PPH: 14% (1/7) Normal baseline clotting factor levels: - Primary PPH: 0% (0/13) - Secondary PPH: 0% (0/13)	Primary PPH treatment consisted of red cell transfusion. Secondary PPH required clotting factor concentrates. These occurred in the same woman.
Wolf, 2020 [57]	HA (N = 16) HB (N = 8)	HA - Primary PPH: 63% (10/16) HB - Primary PPH: 25% (2/8)	None of the included delivery was covered by prophylaxis due to the rise of clotting factor levels above 50 IU/dL.
Chi, 2009 [54]	HA (N = 10) HB (N = 5)	Not available	Prophylactic treatment was not provided for any of the HA and consisted of clotting factor concentrates for 4 HB.
Hawke, 2016 [52]	HA (N = 11)	Total cohort including VWD, factor X deficiency and platelet function defects: - Primary PPH: 18% (11/62) - Secondary PPH: 29% (18/62)	One women (unspecified bleeding disorder) required a blood transfusion due to PPH. No hemophilia carrier received prophylactic treatment. Unknown number of carriers received tranexamic acid upon discharge.  No PPH treatment strategy described, other than prolonged tranexamic acid use in one woman (unspecified bleeding disorder).
			Thirty-six patients (58%) across the complete bleeding disorder cohort were treated with the antifibrinolytic tranexamic acid, significantly reducing

(continued on next page)

**Table 2 (continued)**

Author, year	Number of included deliveries	Incidence PPH (% (N PPH/N total deliveries))	Management strategy (prophylactic, PPH treatment)
Altisent, 2011 [55]	HA (N = 3)	Not available	secondary PPH ( $P < 0.049$ ). No thrombotic complications from tranexamic acid use. Not available

HA = Hemophilia A, HB = Hemophilia B, PPH = Postpartum hemorrhage, VWD = Von Willebrand Disease.

**3.1.3. PPH in relation to mode of delivery**

In the individual patient data, the mode of delivery was described for 85% (90/106) of deliveries and consisted of 44% (40/90) spontaneous vaginal deliveries, 11% (10/90) assisted vaginal deliveries and 44% (40/90) cesarean sections (16 planned, 14 emergency setting, others unknown). PPH occurred in 83% (25/30) of cesarean sections compared to 60% (26/43) of vaginal deliveries (OR: 0.31, 95% CI: 0.10–0.95,  $p = 0.04$ ).

One cohort study examined the relationship between PPH and mode of delivery. [50] Herein the PPH incidence was 6% (5/81) in vaginal deliveries, 22% (2/9) in assisted vaginal deliveries, 63% (5/8) in

elective cesarean sections and 26% (5/19) in emergency cesarean sections.

**3.1.4. PPH management and outcome**

Information on treatment of PPH was available for 68 deliveries in the individual patient data and mostly consisted of clotting factor concentrates and blood products (52% (12/23) and 44% (10/23) respectively, Supplementary Fig. S5). Two women required interventions due to excessive bleeding: one woman underwent uterine artery embolization [44] and another woman underwent a laparotomy twice and was admitted to the intensive care unit (ICU) [59]. No maternal deaths due to PPH were described.

Six cohort studies described the PPH management strategies used (Table 2). [18,50,53,54,58,60] These most commonly included blood transfusions, IV oxytocin and less commonly clotting factor concentrates, cryoprecipitate, carboprost (prostaglandins) and tranexamic acid. DDAVP is not mentioned as a PPH management strategy. In the cohorts, no data on surgical or radiological interventions, ICU admissions were provided. No maternal deaths due to PPH were described.

**3.2. Neuraxial techniques**

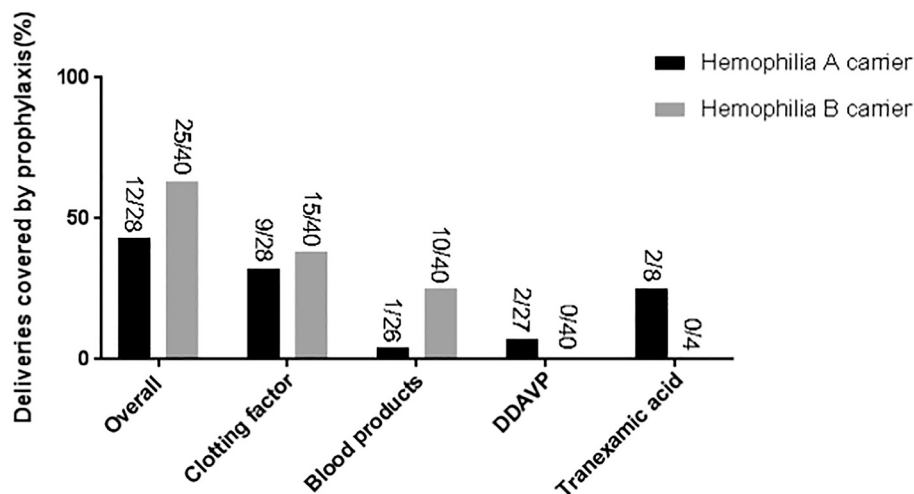
The use of neuraxial techniques was reported in 14% (3/22) of the

**Table 3**

Quality assessment of included studies by Chambers scale according to the number of included patients.

Study population size*	Number of publications	Percentage of studies in which criteria is fulfilled							
		1 were selection/eligibility criteria adequately reported? (% yes)	2 was the selected population representative of that seen in normal practice? (% yes)	3 was an appropriate measure of variability reported? (% yes)	4 was loss to follow-up reported or explained? (% yes)	5 were at least 90% of those included at baseline followed up? (% yes)	6 were patients recruited prospectively? (% yes)	7 were patients recruited consecutively? (% yes)	8 did the study report relevant prognostic factors? (% yes)
1–10 patients included	18	11.1	11.1	11.1	0.0	0.0	0.0	0.0	77.8
11–50 patients included	4	100.0	75.0	100.0	0.0	0.0	25.0	0.0	75.0
51–158 patients included	6	100.0	100.0	100.0	50.0	50.0	16.7	66.7	100.0

Overall quality rating: 'good' (if the answer is 'yes' to all of criteria), 'satisfactory' (if the answer is 'yes' to criteria 2, 4–7; 'poor', (if the answer is not 'yes' to one or more of the criteria listed for 'satisfactory'). Here overall quality is 'poor', with two articles scoring 'satisfactory' and article as 'good'. \*Patients included refers to entire study population. References: 18 Publications [18,33–35,37–44,46–49,55,59], 4 publications [36,53,54,57] and 6 publications [17,50–52,56,58].



**Fig. 2.** Prophylaxis administered for carriers of hemophilia.

Women who received multiple categories of prophylactic treatment are registered multiple times. This data is retrieved from individual case descriptions. The denominator reflects the number of carriers for whom this information was provided in the original article. Blood products = fresh frozen plasma, red blood cell transfusions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

individual patient data deliveries, which in all three cases consisted of epidural anesthesia without local bleeding complications. [38,40,48]

Five cohort studies reported on obstetric analgesia and anesthesia ( $n = 138$ ). [18,50,53,54,57] Of 50 anesthetic procedures, 48 were not covered by prophylaxis (due to a clotting factor levels  $>50$  IU/dL), 3 procedures were not covered by prophylaxis despite clotting factors  $<50$  IU/dL and two procedures were covered by prophylaxis (clotting factor level was  $<50$  IU/dL at term). Nau et al. described 88 anesthetic procedures with factor levels  $>50$  IU/dL at term, of which an unknown percentage had received prophylaxis, and six deliveries with clotting factor levels  $<50$  IU/dL who did not receive neuraxial anesthesia despite prophylactic treatment with increased levels  $>50$  IU/dL. [50] No local bleeding complications were reported in any of the cohort studies.

### 3.3. Neonatal outcome in relation to management

Neonatal bleeding was described in 12% (3/25) deliveries of the individual patient data. These concerned in all three cases cephalohematomas of which one was associated with assisted vaginal delivery, two occurred after emergency cesarean sections, whereas in none of the cases scalp electrodes were used. All three male neonates had hemophilia and in 1/3 this was known before delivery [18,53] No further data on other risk factors, such as preterm delivery, for the occurrence of these cephalohematomas were provided. For the 22 neonates without bleeding complications, gender and successive hemophilia status was only specified in a few cases.

In five cohort studies, information regarding the absence or presence of neonatal bleeding complications was available for 121 neonates. A total of 6 bleeding complications were reported: two cephalohematomas, one subgaleal hematoma and one subependymal hemorrhage after an (emergency) cesarean section [18,50,53], one intracranial hemorrhage after normal vaginal delivery [50] and another one after an assisted vaginal delivery [18]. Of these 6 cases, 2 neonates were known to be affected prepartum. No other neonatal bleeding complications were mentioned.

## 4. Discussion

This systematic review provides an overview of all published data on peripartum management strategies for 502 deliveries in hemophilia carriers, reporting on maternal bleeding complications and in 121 deliveries also on neonatal bleeding outcomes. The high risk of primary and secondary PPH for hemophilia carriers, including the ongoing high risk for women who receive prophylactic treatment, seems apparent.

This review conducted an extensive search for studies in multiple electronic databases. All stated cut-off values for prophylactic treatment were  $< 50$  IU/dL, enabling comparison between studies. By including articles published in several languages, we expanded our reach. Limitations are linked to the available type of evidence and the quality of reporting. Peripartum blood loss is potentially a subjective parameter and is a challenge to estimate. [61] Data mainly originate from case reports, case series and small retrospective cohorts. These study designs are prone to publication bias. Even though some larger studies were included, the incomplete reporting on management strategies hampered thorough analysis on their effectiveness to prevent PPH.

Clotting factor concentrates were the most common method of clotting factor correction, as recommended by international guidelines (e.g. the WFH guidelines, Pavord et al.), but the optimal peripartum management strategy for preventing PPH remains undetermined. [62,63] Recommendations to prevent PPH in carriers are currently based on expert opinion. [12,21,22,64] Both the individual patient- and cohort data in this review provide a limited view of the specific peripartum management strategies used. Mostly, hematologic preventive measures are reported, but information on obstetric prophylactic management strategies is lacking.

The included studies provide insight into the heterogeneity of the

deliveries from hematologic and obstetrical point of view. Obstetrical diversity within the included population is evident since common risk factors for PPH, such as uterus atony, prolonged labor and retained placenta, were mentioned in several PPH cases. [11] Distinguishing between outcomes related to the underlying bleeding disorders or the obstetrical component is problematic. For example, the limited data on emergency versus planned cesarean sections hampers this assessment. Ideally, peripartum care combines careful hematologic preparation and close monitoring plus a fast obstetric as well as hemostatic responses when PPH is impending. [65]

The cohort data show a trend towards an increased risk of primary PPH for those women receiving prophylaxis compared to the women without, whereas the pooled results from the case descriptions appear to find the opposite. The cohort data is more likely to be closer to the true PPH incidence considering the publication bias that case descriptions are prone for. It should be acknowledged however that the largest cohort study was conducted in France and two of the major included Dutch cohort studies originate from the same timeframe within the Netherlands, greatly influencing the PPH results, possibly hampering external validity. Furthermore, there was a large difference in primary PPH incidence in both the general population and the HCs between the Dutch cohort studies and the French cohort study. In the French study by Nau et al., measurement methods of peripartum blood are not described whereas this PPH assessment was based on visual estimates in the Dutch cohort studies, compromising reliability of the PPH data. Nevertheless, overall a higher PPH incidence than seen in general population is evident, regardless of study type, country and prophylactic clotting factor level correction. [10,11] This suggests that current clotting factor correction is not adequate to prevent PPH. Higher clotting factor levels and prolonged patient tailored administration might be options to prevent bleeding. In addition, the high PPH incidence in the non-prophylactic group of this review suggests that more hemophilia carriers could benefit from preventive treatment. Options include increasing the cut-off level for prophylaxis or prolonging prophylaxis duration. In addition, hemophilia carriers are at increased risk to develop secondary PPH, which deserves greater attention and might be reduced by preemptive tranexamic acid use after delivery. [52]

Neuraxial anesthesia appears to be safe when clotting factor levels are  $>50$  IU/dL, since no local bleeding complications occurred. However, it should be noted that the complication of an epidural haematoma is very rare, thus patient numbers are too low to ensure safety. [50,54,62,66–68]

Although less data is present on neonatal outcomes in this review, the increased bleeding risk seems associated with assisted vaginal deliveries and emergency cesarean sections. Previous larger studies, which focus on neonatal outcomes instead of hemophilia carriers, confirm the association with assisted vaginal delivery and offer more detailed insight in neonatal management and outcome. [24–26] No randomized studies have been executed to investigate whether an elective cesarean section or vaginal delivery is safer for an (potentially) affected son. [69] However, intracranial hemorrhage has been seen in both vaginal deliveries and cesarean section, concordant with the results of this review. [24–26] Consequently, it remains preferable to avoid assisted vaginal delivery if possible and the pros and cons of an elective cesarean section should be discussed by healthcare providers with the hemophilia carrier to make a shared decision. [62] The high cesarean section rate (44% in individual data and 23% in the cohort study) in this review might be a reflection of this debate favoring a CS in many cases, but this is not without risks for the mother, especially regarding PPH and future pregnancies. [70]

## 5. Conclusion

Overall poor quality evidence is available on peripartum management of carriers of hemophilia and therefore optimal peripartum management to prevent PPH remains to be elucidated by conducting larger prospective cohort studies. In 502 deliveries by hemophilia carriers

reported in literature, the high risk for PPH seems apparent in hemophilia carriers. Prophylactic treatment to correct clotting factor levels and tranexamic acid use may attenuate this risk.

## 6. Future considerations

Since current prophylactic treatment schedules do not seem to protect hemophilia carriers enough to prevent PPH, intensification of prophylactic management strategies during and after delivery seems prudent. Herein, there could be a role to aim for higher, more physiological, through and/or peak levels of FVIII and FIX during and after delivery, as in normal pregnancy. [71] The development of FVIII levels in the days/weeks after delivery are to be explored, as well as the optimal target FVIII levels during prophylaxis. Furthermore, aggressive obstetric management, such as obligatory use of uterotonic agents during the 3rd stage of labor is required. [62] Finally, mandatory use of tranexamic acid in carriers with a bleeding tendency and/or mild hemophilia is likely to be helpful to prevent primary as well as secondary PPH. [52,72] We are currently conducting a prospective observational study on pregnancy outcomes in hemophilia carriers aiming at a FVIII and FIX peak level of 150 IU/dL at delivery and mandatory use of tranexamic acid postpartum in combination with standard use of uterotonics. This will hopefully shed more light on these issues in the near future (PRIDES study, Dutch trial registry number NL6770).

### 6.1. Research agenda

- Larger prospective studies are needed to acquire more knowledge on the optimal preparation for deliveries in hemophilia carriers.
- Both publication and selection bias needs to be minimized to thoroughly investigate the associated risks, for example hyponatremia due to DDAVP use, thrombosis after intensified clotting factor concentrate prescription, and outcome of different management options.
- National -and preferably international collaboration- is needed to collect sufficient data on available management strategies and outcome of pregnancy. Only then, guidelines can be updated according to evidence based medicine to lower both the peripartum maternal and neonatal bleeding risks.

### 6.2. Practice points

- In hemophilia carriers close obstetric monitoring is warranted due to the high risk for primary and secondary PPH.
- Intensification of prophylactic treatment seems prudent to prevent PPH.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.blre.2021.100826>.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of Competing Interest

The authors have no conflict of interest related to this review.

## Acknowledgements

We would like to acknowledge the valuable support of Bianca Kramer (UMC Utrecht Librarian) regarding the search string for the databases and Pauline Heus (Cochrane) for her advice on our protocol.

## References

- [1] Stonebraker JS, Bolton-Maggs PHB, Michael Soucie J, Walker I, Brooker M. A study of variations in the reported haemophilia a prevalence around the world. *Haemophilia* 2010;16:20–32.
- [2] Plug I, Mauser-Bunschoten EP, Bröcker-Vriens AHJT, Van Amstel HKP, Van Der Bom JG, Van Diemen-Homan JEM, et al. Bleeding in carriers of hemophilia. *Blood* 2006;108:52–6.
- [3] Kadir RA, James AH. Reproductive health in women with bleeding disorders. *Treat Hemoph - WFH Reports* 2009;48:1–20.
- [4] Nisen P, Stamberg J, Ehrenpreis R, Velasco S, Shende A, Engelberg J, et al. The molecular basis of severe hemophilia B in a girl. *N Engl J Med* 1986;315:1139–42.
- [5] Miesbach W, Alesci S, Geisen C, Oldenburg J. Association between phenotype and genotype in carriers of haemophilia a. *Haemophilia* 2011;17:246–51.
- [6] Chee Y, Townend J, Crowther M, Smith N, Watson H, Chee YL, et al. Assessment of von Willebrand disease as a risk factor for primary postpartum haemorrhage. *Haemophilia* 2012;18:593–7.
- [7] De Wee E, Knol H, Mauser-Bunschoten E, Van Der Bom J, Degenaar-Dujardin M, Eikenboom J, et al. Gynaecological and obstetric bleeding in moderate and severe Von Willebrand disease. *Thromb Res* 2011;127:S129.
- [8] van Kujovich J. Willebrand disease and pregnancy. *J Thromb Haemost* 2005;3:246–53.
- [9] Mauser Bunschoten EP, van Houwelingen JC, Sjamsoedin Visser EJ, van Dijken PJ, Kok AJ, Sixma JJ. Bleeding symptoms in carriers of hemophilia a and B. *ThrombHaemost* 1988;59:349–52.
- [10] Zwart JJ, Richters JM, Öry F, De Vries JJP, Bloemenkamp KWM, Van Roosmalen J. Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: a nationwide population-based study of 371 000 pregnancies. *BJOG An Int J Obstet Gynaecol* 2008;115:842–50.
- [11] Bais J, Eskes M, Pel M, Bonsel G, Bleker O. Postpartum haemorrhage in nulliparous women: incidence and risk factors in low and high risk women: a Dutch population-based cohort study on standard ( $\geq 500$  ml) and severe ( $\geq 1000$  ml) postpartum haemorrhage. *Eur J Obstet Gynecol Reprod Biol* 2004;115:166–72.
- [12] Demers C, Derzko C, David M, Douglas J. Gynaecological and obstetric management of women with inherited bleeding disorders. *J Obstet Gynaecol Can* 2018;40:e91–103.
- [13] Huq FY, Kulkarni A, Agbim EC, Riddell A, Tuddenham E, Kadir RA. Changes in the levels of factor VIII and von Willebrand factor in the puerperium. *Haemophilia* 2012;18:241–5.
- [14] Uchikova EH, Ledjev II. Changes in haemostasis during normal pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2005;119:185–8.
- [15] Szeeci P, Jørgensen M, Klajnbar A, Andersen M, Colov N, Stender S. Haemostatic reference intervals in pregnancy. *Thromb Haemost* 2010;103:718–27.
- [16] Castaman G. Changes of von Willebrand factor during pregnancy in women with and without von Willebrand disease. *Mediterr J Hematol Infect Dis* 2013;5:e2013052.
- [17] Stoof SCM, van Steenberg HW, Zwagemaker A, Sanders YV, Cannegieter SC, Duvekot JJ, et al. Primary postpartum haemorrhage in women with von Willebrand disease or carriership of haemophilia despite specialised care: a retrospective survey. *Haemophilia* 2015;21:505–12.
- [18] Chi C, Lee CA, Shiltagh N, Khan A, Pollard D, Kadir RA. Pregnancy in carriers of haemophilia. *Haemophilia* 2008;14:56–64.
- [19] James AH, Cooper DL, Paidas MJ. Hemostatic assessment, treatment strategies, and hematology consultation in massive postpartum hemorrhage: results of a quantitative survey of obstetrician-gynecologists. *Int J Women's Health* 2015;7:873–81.
- [20] James AH, Manco-Johnson MJ, Yawn BP, Dietrich JE, Nichols WL. Von Willebrand disease: key points from the 2008 National Heart, Lung, and Blood Institute guidelines. *Obstet Gynecol* 2009;114:674–8.
- [21] Nichols WL, Hultin MB, James AH, Manco-Johnson MJ, Montgomery RR, Ortel TL, et al. von Willebrand disease (VWD): Evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) expert panel report (USA). *Haemophilia* 2008;14:171–232.
- [22] Lee CA, Chi C, Pavord SR, Bolton-Maggs PHB, Pollard D, Hinchcliffe-Wood A, et al. The obstetric and gynaecological management of women with inherited bleeding disorders—review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2006;12:301–36.
- [23] Shakur H, Roberts I, Fawole B, Chaudhri R, El-Sheikh M, Akintan A, et al. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017;389:2105–16.
- [24] Davies J, Kadir RA. Mode of delivery and cranial bleeding in newborns with haemophilia: a systematic review and meta-analysis of the literature. *Haemophilia* 2016;22:32–8.
- [25] Kulkarni R, Presley RJ, Lusher JM, Shapiro AD, Gill JC, Manco-Johnson M, et al. Complications of haemophilia in babies (first two years of life): a report from the Centers for Disease Control and Prevention universal data collection system. *Haemophilia* 2017;23:207–14.
- [26] Richards M, Lavigne Lissalde G, Combescore C, Batorova A, Dolan G, Fischer K, et al. Neonatal bleeding in haemophilia: a European cohort study. *Br J Haematol* 2012;156:374–82.
- [27] <https://www.crd.york.ac.uk/prospero/>.
- [28] Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP, Oxman A, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.



- [29] Higgings J. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane Handbook for Systematic Reviews of Interventions. Version 5. The Cochrane Collaboration. 2011.
- [30] Punt MC, Waning ML, Mauser-Bunschoten EP, Kruip MJHA, Eikenboom J, Nieuwenhuizen L, et al. Maternal and neonatal bleeding complications in relation to peripartum management in women with Von Willebrand disease: a systematic review. *Blood Rev* 2020;39:100633.
- [31] Dekkers OM, Egger M, Altman DG, Vandembroucke J. Distinguishing case series from cohort studies. *Ann Intern Med* 2013;1–10.
- [32] Chambers D, Rodgers M, Woolacott N. Not only randomized controlled trials, but also case series should be considered in systematic reviews of rapidly developing technologies. *J Clin Epidemiol* 2009;62: 1253–1260.e4.
- [33] Baty BJ, Drayna D, Leonard CO, White R. Prenatal diagnosis of factor VIII deficiency to help with the management of pregnancy and delivery. *Lancet* 1986;1: 207.
- [34] Bodrozic J, Miljic P, Lekovic D, Petronijevic M, Antic D, Mitrovic M, et al. Pregnancy and delivery in a woman with severe haemophilia A. *Blood Coagul Fibrinolysis* 2017;28:496–9.
- [35] Seeds JW, Cefalo RC, Miller DT, Blatt PM. Obstetric care of the affected carrier of hemophilia B. *Obstet Gynecol* 1983;62:23s–5s.
- [36] Yang MY, Ragni MV. Clinical manifestations and management of labor and delivery in women with factor IX deficiency. *Haemophilia* 2004;10:483–90.
- [37] Briet E, Reischer HM, Blatt PM. Factor IX levels during pregnancy in a woman with hemophilia B. *Haemostasis* 1982;11:87–9.
- [38] Skatvold S. Placement of labor epidural in hemophilia a carrier. *Int Student J Nurse Anesth* 2012;11:15–8.
- [39] Gekas J, Broermann L, Heidenreich W. Outcome of pregnancy in patients with haemophilia B - two case reports. *Z Geburtshilfe Neonatol* 2007;211:90–2.
- [40] Dhar P, Abramovitz S, DiMichele D, Gibb C, Gadalla F. Management of pregnancy in a patient with severe haemophilia a. *Br J Anaesth* 2003;91:432–5.
- [41] Sharma V, Khalid A, Cohen AJ. Management of pregnancy in a patient with severe hemophilia type a. *AJP Rep* 2013;3:29–32.
- [42] Bonnet A, Chevalier Y, Wallon G, Huissoud C, Aubrun F. Peripartum period and hemophilia carriers. *Ann Fr Anesth Reanim* 2013;32:807–10.
- [43] Gilchrist GS, Wilke JL, Muehlenbein LR, Danilenko-Dixon D. Intrauterine correction of factor VIII (FVIII) deficiency. *Haemophilia* 2001;7:497–9.
- [44] Malin G, Swallow G, Rutherford J. Two rare risk factors for post-partum haemorrhage: a case report of a carrier of severe haemophilia a with a uterine arteriovenous malformation. *J Obstet Gynaecol (Lahore)* 2017;37:948–9.
- [45] Takahashi H, Hayashi N, Shibata A. Type IB von Willebrand's disease and pregnancy: comparison of analytical methods of von Willebrand factor for classification of von Willebrand's disease subtypes. *Thromb Res* 1988;50:409–18.
- [46] Orstavik K, Stormorken H, Sparr T. Hemophilia B(M) in a female. *Thromb Res* 1985;37:561–6.
- [47] Przkora R, Euliano TY, Roussos-Ross K, Zumberg M, Robicsek SA. Labor and delivery in a patient with hemophilia B. *Int J Obstet Anesth* 2011;20:250–3.
- [48] Russell Z, Riconda D, Pollack L, O'Leary TD, Carlan SJ. Thrombosis in a pregnant hemophilia a carrier after intrapartum recombinant factor VIII. *Obstet Gynecol* 2005;105:875–6.
- [49] Rust LA, Goodnight SH, Freeman RK, Johnson CS. Pregnancy and delivery in a woman with hemophilia B. *Obstet Gynecol* 1975;46:483–6.
- [50] Nau A, Gillet B, Guillet B, Beurrier P, Ardillon L, Cussac V, et al. Bleeding complications during pregnancy and delivery in haemophilia carriers and their neonates in Western France: an observational study. *Haemophilia* 2020;1–10.
- [51] Greer IA, Lowe GD, Walker JJ, Forbes CD. Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. *Br J Obstet Gynaecol* 1991;98:909–18.
- [52] Hawke L, Grabell J, Sim W, Thibeault L, Muir E, Hopman W, et al. Obstetric bleeding among women with inherited bleeding disorders: a retrospective study. *Haemophilia* 2016;22:906–11.
- [53] Kadir R, Economides D, Braithwaite J, Goldman E, Lee C. The obstetric experience of carriers of haemophilia. *Br J Obstet Gynaecol* 1997;104:803–10.
- [54] Chi C, Lee CA, England A, Hingorani J, Paintsil J, Kadir RA. Obstetric analgesia and anaesthesia in women with inherited bleeding disorders. *Thromb Haemostasis* 2009; 101:1104–11.
- [55] Altisent C, Martorell M, Vidal F, Sanchez MA, Parra R. The optimal mode of delivery for the haemophilia carrier expecting an affected infant: further considerations. *Haemophilia* 2011;17:818–9.
- [56] Zwagemaker A, Gouw SC, Valk C, Ganzevoort W, Coppens M, Peters M. Postpartum haemorrhage in an unselected cohort of carriers of haemophilia. *Haemophilia* 2018;24:e256–9.
- [57] Wolf S, Sardo Infirri S, Batty P, Sahar B, Beski S, Bowles L. Postpartum bleeding in women with inherited bleeding disorders: a matched cohort study. *Blood Coagul Fibrinolysis* 2020;31:452–8.
- [58] Lavin M, Horan M, Durand O'Connor A, Doherty D, Manning C, Lynch C, et al. The impact of foetal restrictions on mode of delivery in women with inherited bleeding disorders. *Eur J Haematol* 2020:1–6.
- [59] Meijer K, Bouman K, Sollie K, Tammirya R, Van Der Meer J. Management of pregnancy and childbirth in carriers of haemophilia. *Ned Tijdschr Geneesk* 2008; 152:1249–53.
- [60] Greer IA, Lowe GD, Walker JJ, Forbes CD. Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. *Br J Obstet Gynaecol* 1991;98:909–18.
- [61] Bose P, Regan F, Paterson-Brown S. Improving the accuracy of estimated blood loss at obstetric haemorrhage using clinical reconstructions. *BJOG An Int J Obstet Gynaecol* 2006;113:919–24.
- [62] Pavord S, Rayment R, Madan B, Cumming T, Lester W, Chalmers E, et al. Management of Inherited Bleeding Disorders in pregnancy: green-top guideline no. 71 (joint with UKHADO). *BJOG* 2017;124:e193–263.
- [63] Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia* 2020:1–158.
- [64] James AH. Guidelines for bleeding disorders in women. *Thromb Res* 2009;123 (Suppl):S124–8.
- [65] Dahlke J, Mendez-Figueroa H, Maggio L, Hauspurg A, Sperling J, Chauhan S, et al. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. *Am J Obstet Gynecol* 2015;213:76.e1–76.e10.
- [66] Choi S, Brull R. Neuraxial techniques in obstetric and non-obstetric patients with common bleeding diatheses. *Anesth Analg* 2009;109:648–60.
- [67] Moen V, Irestedt L. Neurological complications following central neuraxial blockades in obstetrics. *Curr Opin Anaesthesiol* 2008;21:275–80.
- [68] Harrop-Griffiths W, Cook T, Gill H, Hill D, Ingram M, Makris M, et al. Regional anaesthesia and patients with abnormalities of coagulation: the Association of Anaesthetists of Great Britain & Ireland the Obstetric Anaesthetists' Association regional Anaesthesia UK. *Anaesthesia* 2013;68:966–72.
- [69] Karanth L, Kanagasabai S, Abas ABL. Maternal and foetal outcomes following natural vaginal versus caesarean section (c-section) delivery in women with bleeding disorders and carriers. *Cochrane Database Syst Rev* 2017;8:CD011059.
- [70] Keag OE, Norman JE, Stock SJ. Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: systematic review and meta-analysis. *PLoS Med* 2018;15:1–22.
- [71] Szecei PB, Jørgensen M, Klajnbard A, Andersen MR, Colov NP, Stender S. Haemostatic reference intervals in pregnancy. *Thromb Haemostasis* 2010;103:718–27.
- [72] Li C, Gong Y, Dong L, Xie B, Dai Z. Is prophylactic tranexamic acid administration effective and safe for postpartum hemorrhage prevention? A systematic review and meta-analysis. *Medicine (Baltimore)* 2017;96:e5653.