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Review

Maternal and neonatal bleeding complications in relation to peripartum management in women with Von Willebrand disease: A systematic review

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ABSTRACT

Women with Von Willebrand disease (VWD) have an increased risk of developing postpartum hemorrhage (PPH). Our aim is to evaluate peripartum management strategies in relation to maternal and neonatal bleeding complications in VWD. Electronic databases were searched up to January 2019. Seventy-one case-reports and -series and 16 cohort studies were selected, including 811 deliveries. Cohort studies reported primary PPH in 32% and secondary PPH in 13% of the women. The overall primary PPH incidence in the individual patient data was 34%, similar between women who received prophylactic treatment to prevent PPH and those who didn't. Neonatal bleeding events were reported in 4.6% of deliveries. Overall, the available evidence on peripartum management in women with VWD was of low quality. The ongoing high risk for PPH is evident, despite prophylactic treatment, as well as the need for higher quality evidence from larger prospective cohort studies to improve management strategies.

1. Introduction

The most common inherited bleeding disorder is Von Willebrand disease (VWD). In VWD, the Von Willebrand factor (VWF)-antigen level can be too low (VWD type 1), absent (VWD type 3) or dysfunctional (VWD type 2), resulting in decreased VWF-activity. Women with VWD, depending on the subtype of their disease and its severity, might need prophylactic treatment to prevent bleeding events. These potentially include

prolonged bleeding after trauma, heavy menstruation and potential excessive postpartum blood loss (postpartum hemorrhage, PPH) [1].

In healthy pregnant women, hemostasis is changed into a procoagulant state to prepare for childbirth. This procoagulant state is the result of an increase in clotting factor levels and a decrease in anticoagulant clotting factors [2,3]. VWF levels also increase during pregnancy in patients with VWD type 1. In VWD type 2, there is an increase in dysfunctional VWF-antigen, without increase of the VWF-activity.

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VWD type 3 shows no rise in VWF during pregnancy [4,5]. In the postpartum period, VWF and FVIII levels approach baseline pre-pregnancy levels within one week [6]. Thus, the absence- or incomplete-preparation of the hemostatic system during pregnancy leaves these women at an increased risk of bleeding complications during childbirth and the postpartum period [7].

Guidelines and expert papers on the management of pregnancy of women with VWD recommend timely preparation of an individualized delivery plan [8–11]. Clotting factor levels have to be monitored during the third trimester of pregnancy. Potential prophylactic management consists of clotting factor concentrates, blood products and desmopressin (DDAVP), which aims to increase the maternal clotting factor levels. In addition, the antifibrinolytic agent tranexamic acid can be administered to inhibit fibrinolysis [7,12]. The other key factors for a safe delivery depend on the (potentially) affected child. Delivery of a (potentially) affected neonate contraindicates invasive procedures during delivery including fetal blood sampling and operative vaginal deliveries, such as vacuum extraction and forceps [13].

PPH remains a worldwide, main cause of severe maternal morbidity and mortality. Women with VWD have been found to be at an increased risk of PPH with a prevalence of 20–51% being reported, even with the current standard of care [14–17]. This prevalence of PPH vastly exceeds the mean PPH prevalence seen in the general population of 19% [18,19]. However, guidelines for peripartum management for women with VWD are mainly based on expert opinion [20]. In view of the increased risk of PPH for women with VWD 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 women with VWD and their relation to maternal and neonatal bleeding complications.

2. Methods

2.1. Protocol and registration

This systematic review was registered at PROSPERO (CRD42018091987) [21] and conducted according to Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines and Cochrane methodology [22,23]. The literature search was combined with a systematic review on hemophilia carriers – however during the data analysis phase, the decision was made to present the data in two separate papers due to the amount of the reported data and the difference in hemostatic defect.

2.2. Review questions

This review aims to answer the following research questions for women with VWD:

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

2.3. Eligibility criteria

Observational and intervention studies concerning peripartum management for women with VWD were eligible for inclusion. These studies included women who are known to have VWD during pregnancy. Only articles written in English, German, French or Dutch were included. Only studies containing original patient data published as full papers in peer reviewed journals were eligible.

2.4. Information sources and search

The electronic search for both reviews was combined and conducted up to January 1st of 2019 in the following databases: Pubmed/

MEDLINE, The Cochrane Library, EMBASE and CINAHL. Each search string used pre-defined search (Title and Abstract) and MeSH/Emtree terms related to VWD, hemophilia and peripartum management (Supplement S1: Full search string all databases). Both electronic and hard-copies were searched. No limits were used.

2.5. Study selection

After combining the search results, duplicates were removed by Mendeley reference software and by hand. 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. Authors were contacted once in case of inaccessible full-texts. Cross-referencing the bibliography of the included studies was conducted to find additional studies that could have been missed during the primary search.

2.6. Data collection process

Data extraction was conducted by two independent authors (MCP and MW) using a standardized data extraction sheet (Supplement S2: Data extraction sheet). Main parts of the data extraction sheet covered information on the study design, patient characteristics, peripartum management (prophylactic treatment to prevent PPH and therapeutic treatment of PPH), in addition to both maternal and neonatal bleeding complications. Primary PPH was defined as blood loss of 500 ml or more within 24 h and secondary PPH as excessive vaginal 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. Study design was based upon the following criteria: a cohort study in case all eligible patients during a certain time period were included into the study, and a case series if patient selection was not described [24]. Outcome measurements were noted as counts in case of individual data and as counts *and* percentages in cohort studies if available or possible to calculate. The corresponding author was contacted once in case of incomplete data. In case of disagreements during the extraction process, a third author was consulted (KG).

2.7. Risk of bias assessment

Risk of bias was assessed for each study using the Chambers scale (Supplement S3: Chambers quality assessment). This scale was chosen to be the most informative as most included studies were case series and only one included cohort reported a control cohort. Risk of bias assessment was conducted by two independent authors (MCP and MW) [25]. The overall Chambers quality rating of studies is divided into, 'good', 'satisfactory' or 'poor'. Any disagreement was resolved by consulting a third author (KG). Risk of bias across studies could not be assessed through a funnel plot or Egger's tests due to heterogeneity in population and study outcomes.

2.8. Data synthesis

The quantitative results of all studies were summarized according to the available results: individual cases descriptions and overall data. A descriptive overview was created for prophylactic treatment and occurrence of primary and secondary PPH. Insufficient data were available for any subgroup analyses on subtypes of VWD. A narrative synthesis is provided on treatment (prophylactic and therapeutic for PPH), incidence of PPH, neuraxial techniques and additional outcomes.

3. Results

A total of 6751 articles were obtained after duplicate removal and inclusion of the three additional papers found by cross-reference

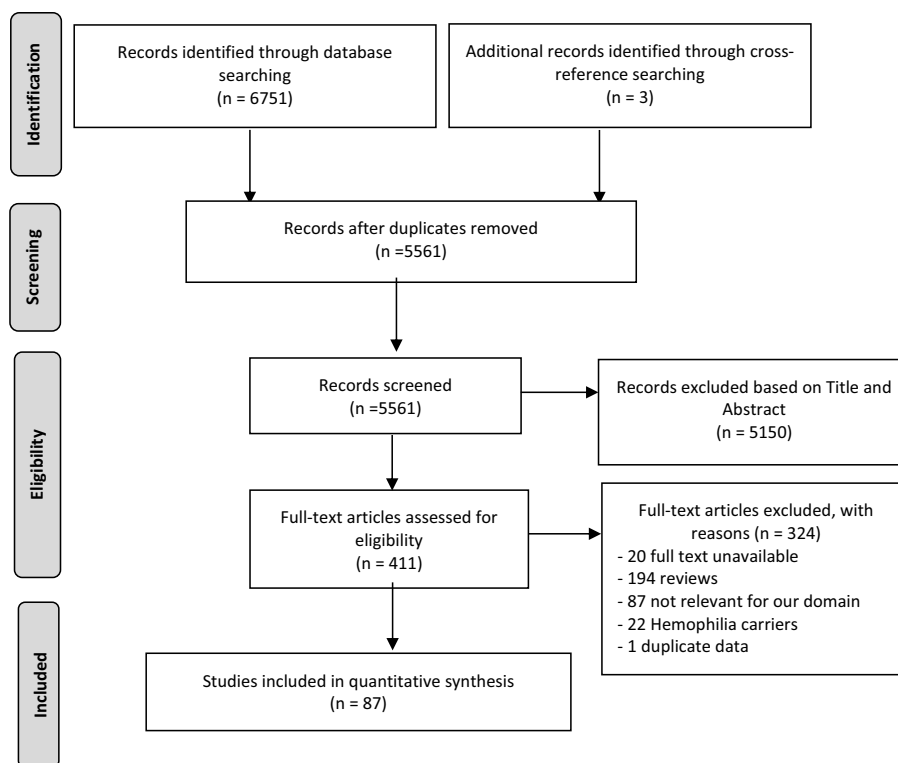


Fig. 1. Prisma Flowchart for identifying eligible studies on peripartum management for women with Von Willebrand Disease.

searching (Fig. 1). After title and abstract screening, 411 articles were selected for full-text assessment. The final selection consisted of 87 articles: 71 case reports [26–95] and 16 cohort studies [96–111]. A total of 811 deliveries from women with VWD were reported. An overview of the reported deliveries per study type can be found in Table 1.

3.1. Risk of bias of studies

A summary of quality assessment on each domain for all included studies is provided in Table 2 for small, medium and large size studies. Detailed quality assessment of each individual study is provided in Supplement S4: Quality assessment per study. The quality of the

Table 1
Number of published deliveries per study type.

		Individual case descriptions	Cohort	Total
		N	N	
Von Willebrand Disease	Total	365	619	811 [†]
	Unknown [‡]	115	218	282 [^]
	T1 [*]	104	208	239 [^]
	T2 Unknown	33	27	40 [^]
	T2A	38	42	58 [^]
	T2B [^]	34	13	44 [^]
	T2M	12	3	15
	T2N	9	6	14 [^]
	T3 [^]	20	102	119 [^]

Legend: ^{*}T = Type, [‡]Unknown = Unknown subtype, N = number of reported deliveries. [^]The following women are mentioned twice: 51 VWD Type unknown [99,107,117], 73 VWDT1 [91,96,97,99,109,118,119], 20 VWDT2 [99,106,118,119], 22 VWDT2A [96,99,109,118], 3 VWDT2B [99], 1 VWDT2N [96] and 3 VWDT3 [99]. [†]Total deliveries: double entries omitted. [^]Alloantibodies present in 7 T3 deliveries [31,52,59,89] and 4 antibodies present in 4 T2B [28,63,86].

References: [26–111].

included studies was rated as ‘poor’, according to the Chambers scale in 100% of included papers since none of the papers reported on follow up or missing data.

3.2. Narrative synthesis of quantitative results

Fig. 2 shows a summary of the occurrence of bleeding complications regarding the individual patient data. Table 3 shows the bleeding complications in the cohort data. Detailed results on study design, characteristics of included patients, peripartum management and both maternal – and neonatal outcomes can be provided on request.

The cut off level of FVII and VWF activity for prophylaxis was mentioned in 24 articles [27,32,39,41–43,48,52,56–58,64,72,77,82,85,88,93,101,105,108,110]. The range was 30 to 60 IU/dL of third trimester clotting factor levels [32,39,41,56,64,82], with the majority of articles following a cut off value of 50 IU/dL [27,42,43,48,52,57,58,72,77,85,88,93,101,105,108]. However, in one article prophylactic management (cryoprecipitate and fresh plasma before and after delivery) [110] and in a second article prophylactic tranexamic acid were always provided [101], in both cases independent of the FVIII/VWF factor level during the third trimester.

3.2.1. Narrative synthesis - individual patient data

Individual patient data was described for 365 deliveries. The mode of delivery was described for 77% (281/365) of deliveries with VWD and consisted of 68% (190/281) atraumatic vaginal deliveries, 6% (18/281) assisted vaginal deliveries and 26% (73/281) caesarean sections (CS).

Information on postpartum blood loss was available in 90% (327/365) of individual deliveries. Fig. 2 depicts PPH per mode of delivery for women with and without prophylactic treatment. Occurrence of PPH was reported in 34% (111/327) of these deliveries. For those women who received (64/206) and those who did not receive (33/108) prophylaxis, the PPH incidence was similar (31%). PPH occurred in 42% (29/69) of CS compared to 34% (65/192) in vaginal deliveries. Prophylactic treatment consisted mostly of clotting factor concentrates,

Table 2
Quality assessment of included studies according to the number of included patients.

Study population size* Number of publications included	Percentage of studies in which criteria is fulfilled									
	Were selection/eligibility criteria adequately reported?	Was the selected population representative of that seen in normal practice?	Was an appropriate measure of variability reported?	Was loss to follow-up reported or explained?	Were at least 90% of those included at baseline followed up?	Were patients recruited prospectively?	Were patients recruited consecutively?	Did the study report relevant prognostic factors?	Comparability of cohorts based on study or analysis?	
1–10 patients included	4,3	4,3	0,0	0,0	0,0	2,9	4,3	92,8	NA	
11–50 patients included	81,8	81,8	81,8	0,0	0,0	36,4	27,3	81,8	100*	
51–158 patients included	83,0	83,0	83,0	0,0	0,0	0,0	0,0	100	NA	

Legend: *The study of James reported a cohort of women without Von Willebrand Disease [99]. Here we adapted the Chambers scale to add the following component on 'Comparability' as derived from the Newcastle Ottawa Scale. Here overall quality is 'poor'. *Patients included refers to entire study population.
References: 70 [26–79,81,82,84–95,98,120], 11[80,83,96,97,99–101,106,107,109,110] and 6[102–105,108,111]

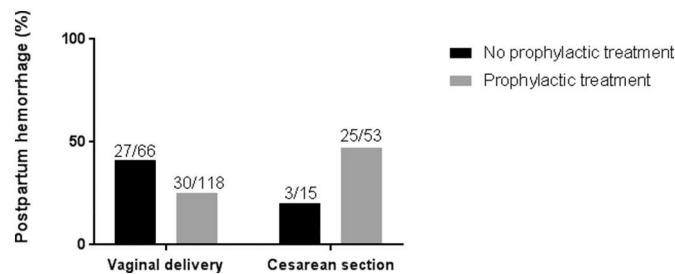


Fig. 2. Occurrence of postpartum hemorrhage in individual case descriptions of women with Von Willebrand Disease.
Legend: $P = .03$ and $P = .07$, respectively.

followed by DDAVP and blood products (Supplement S5: Prophylactic treatment for postpartum hemorrhage). In two women with VWD type 2B, intravenous immunoglobulins and steroids were administered during labor and the postpartum period due to suspicion of immune thrombocytopenic purpura [63,86]. Information on PPH treatment was available for 45 deliveries. Clotting factor concentrates and blood products were most often administered (Supplement S6: Therapeutic treatment for postpartum hemorrhage). Eighty-four percent (38/45) of women required blood products due to PPH, of which 14 required blood transfusions.

Hyponatremia due to DDAVP administration was mentioned in 1% (1/88) of deliveries. DDAVP was administered in 57% (46/81) before cord clamping. One woman (an allo-immunized VWD type 3 patient) developed an iliofemoral venous thrombosis at postpartum day 19 [31] and one woman developed venous thromboembolism (this patient received immunoglobulins; disseminated intravascular coagulation occurred with a pulmonary embolism) [86].

The use of neuraxial techniques was reported in 74% (100/136) of deliveries, of which three were spinal [38,54,100], 92 epidural [27,40,41,44,50,52,81,83,95,97,100,103,109], two combined spinal/epidural [32,46], one lumbar [33], one caudal anesthesia [98] and one unspecified neuraxial technique [66]. One woman was reported to have experienced lumbar bleeding, no other complications were reported [66].

Neonatal bleeding was described in 4% (3/67) of deliveries [66,74,90]. These concerned one cephalhematoma [90] (after emergency CS), one subcutaneous head hematoma [66] (elective CS) and one case of petechial bleeds after birth (spontaneous vaginal delivery, later on diagnosed with VWD type 2) [74].

3.2.2. Narrative synthesis - Cohort data

Sixteen cohort studies reported on 619 deliveries of women with VWD (Table 3) [96–111].

3.2.2.1. Prospective cohort studies. Kadir et al. reported a primary and secondary PPH in 18.5% (10/54) and 20% (11/54) of deliveries in women with VWD, respectively [107]. None of the women who experienced a primary PPH were given prophylactic treatment during delivery. None (0/10) of the women who received prophylactic treatment in labor or puerperium developed a primary or secondary PPH, yet one woman experienced perineal bruising.

The prospective cohort study by James et al. aimed to elucidate the fall in VWF and FVIII activity after childbirth in 35 women with and 40 women without VWD and reported on bleeding and corresponding treatments (Table 3) [99]. Lochial blood loss was assessed by the modified pictorial blood assessment chart and changes in hematocrit or hemoglobin. The recorded lochial blood loss was equivalent to that of women without VWD or untreated VWD women until 3 weeks postpartum. Six weeks postpartum, lochial blood loss was significantly more in VWD women compared to the other women ($P < .01$).

Sood et al. prospectively followed 12 type 1 VWD women to model changes in VWF levels during delivery and the postpartum period, and

Table 3
Summary of outcome data from cohort studies on women with Von Willebrand Disease.

Author, year	Number of included deliveries	Incidence postpartum hemorrhage	Comments
Xu, 2018 [111]	VWD (N = 86)	6/86 Primary PPH 2/86 Secondary PPH	Epidural/spinal anesthesia was administered for 32/86 deliveries (no haemorrhagic complication).
Stoof, 2015 [108]	VWD (N = 71)	VWD type 1: 21/56 PPH VWD type 2: 6/15 PPH	PPH occurred in 50% (10/20) prophylactically treated deliveries.
Lak, 2000 [102]	VWD T3 (N = 100)	15% (15/100) Abnormal bleeding	Deliveries were usually treated with FFP, cryoprecipitate or more recently with FVIII concentrates.
Hawke, 2016 [105]	VWD (N = 47)	Not available	Data on PPH is combined with VWD deliveries. No thrombotic complications from tranexamic acid use.
Kadir, 1998 [107]	VWD (N = 54)	Prophylaxis: 0/ 10 Primary PPH No prophylaxis: 10/44 Primary PPH Unknown prophylaxis: 11/54 Secondary PPH	None of the women who experienced a primary PPH was given prophylactic treatment for labor.
Sanchez-Luceros, 2007 [103]	Low plasmatic VWF + bleeding history (N = 53)	Not available	DDAVP was infused before 5 general anesthesia procedures and 48 epidural blockades). No local complications associated with the epidural placement.
Govorov, 2016 [101]	VWD T1, 2 and 3 (N = 43)	Prophylaxis: 20/43 Primary PPH Prophylaxis: 2/43 Secondary PPH	In all pregnancies tranexamic acid and in all cases either DDAVP or clotting factor concentrates (containing VWF and FVIII) were added.
James, 2015 [99]	VWD (N = 35) No VWD (N = 40)	No prophylaxis: mean EBL = 475 ml, range 332–618 Prophylaxis: mean EBL = 615 ml, range 473–758 No VWD: mean EBL = 437 mL, range 346–529	EBL = Estimated Blood Loss During 18 deliveries no prophylaxis and during 17 deliveries prophylaxis was administered.
Gojnic, 2005 [117]	VWD (N = 32)	No complications occurred	DDAVP was applied in the 36th/37th week of gestation and cryoprecipitate and fresh frozen plasma were applied 1 day before and 3 days after delivery. Factor VIII (Haemate P®) was administered at the day of delivery and every 24 h after delivery for 3 days. DDAVP treatment continued for 4 weeks.
Castaman, 2009 [96]	VWD (N = 31)	4/31 excessive bleeding postpartum	
Varughese, 2007 [109]	VWD T1 (N = 16), T2A (N = 1)	VWD type 1: 7/16 PPH VWD type 2A: 1/1 PPH	None of the women received DDAVP or clotting factor concentrates prior to the administration of epidural anesthesia.
Marrache, 2007 [97]	VWD T1 (N = 16)	0/16 PPH	No anesthetic complications during the 9 procedures.
Chi, 2009 [106]	VWD T1 (N = 11), T2 (N = 2)	Not available	Obstetric analgesia and anesthesia was investigated. A bloody tap in a woman.
Greer 1991 [118]	VWD (N = 11)	2/11 Primary PPH 4/11 Secondary PPH	
Scholz, 2011 [91]	VWD (N = 10)	Prophylaxis: 0/2 bleeding complications No prophylaxis: 0/8 bleeding complications	Prophylaxis consisted of tranexamic acid.

Legend: VWD = Von Willebrand disease, T = Type, VWF = Von Willebrand factor, PPH = Postpartum hemorrhage, FVIII = Factor VIII, DDAVP = desmopressin.

to analyze bleeding complications. All women's VWF levels were > 50% at the time of delivery with a variable rise and fall in levels. Three women were treated with VWF concentrate peri- and postpartum, one due to a history of PPH, one due to low VWF levels and the third for unclear reasons. One case of primary PPH and one case of secondary PPH occurred, however it was not mentioned whether this occurred in the (not) prophylactically treated group [100].

3.2.2.2. Retrospective cohort studies. Xu et al. reported on 86 deliveries by 55 women (29 women with VWD type 1, 25 women with VWD type 2, one woman with VWD type 3) [111]. Prophylactic treatment was administered in 84% (26/31) of deliveries with preterm VWF:RCo and/or FVIII:C levels < 50 IU/dL. VWF concentrates were administered in 23 deliveries; 7 in type 1, 15 in type 2 patients and one in a type 3 patient. DDAVP was administered in two patients with severe type 1 and in one patient with type 2A. Two women received tranexamic acid to prevent PPH. The overall incidence of primary PPH was 6.9% (6/86), including severe primary PPH in three patients (3.5%). In these cases, treatment of obstetric causes stopped the bleeding. Only one patient received blood transfusion. Secondary PPH was observed in two patients (2.3%). Epidural/spinal anesthesia was administered in 37% (32/86) of deliveries, during which no local bleeding complications occurred.

A Dutch retrospective cohort by Stoof et al. reported 86 deliveries by 71 women with VWD [108]. Here, PPH occurred in 37.5% (21/56) of deliveries in VWD type 1 and in 40% (6/15) of VWD type 2

deliveries. PPH occurred in 50% (10/20) of prophylactically treated deliveries due to a VWF activity below the 50 IU/dL cut-off in the third trimester (VWD type 1 and 2 combined).

Govorov et al. provided an overview of 34 women (59 deliveries) with VWD in whom the PPH incidences were as following: primary PPH 44% (26/59), severe primary PPH 20% (12/59) and secondary PPH 12% (7/59) [101]. VWD type 3 was associated with a higher risk of severe primary PPH (> 1000 cc) compared to other VWD subtypes ($P = .02$). In all pregnancies, including those with spontaneous correction of clotting factors, tranexamic acid was prescribed at the start of labor and in all cases either DDAVP or clotting factor concentrates was added.

The retrospective study of Hawke et al. evaluated the pregnancy management in 47 women with VWD [105]. Tranexamic acid use, next to clotting factor replacement, was found to decrease the incidences of delayed PPH significantly in women with inherited bleeding disorders. No thrombotic complications were reported with tranexamic acid use during the postpartum period.

3.2.2.3. Analgesia and DDAVP. Obstetric analgesia and anesthesia was retrospectively reviewed by Chi et al., in 11 women with VWD type 1 and two VWD type 2 [106]. The only bleeding complication reported was a bloody tap in a woman with VWD, but no further complications occurred. Intramuscular pethidine was given without complications in one woman with VWD.

The clinical safety of DDAVP during pregnancy was evaluated by Sanchez-Luceros et al., in women with a low VWF level and bleeding history [103]. In 53 deliveries, DDAVP was infused before anesthesia (5/53 general anesthesia and 48/53 epidural blockade). Local complications associated with epidural placement were not observed. Twenty-two vaginal deliveries were performed without anesthesia, and DDAVP was infused at the onset of labor. There was no hyponatremia in the mothers, and none of the patients presented thromboembolic complications. None of the babies were born prematurely, and neonatal bleeding was not reported.

4. Discussion

This systematic review provides an overview of all published data on peripartum management strategies and maternal bleeding outcomes for 811 deliveries by women with VWD and of 65 neonatal bleeding outcomes. A high incidence of bleeding complications of 34% is reported in women with VWD, independent of the use of prophylactic treatment. Neonatal bleeding incidence was 4%.

The larger cohort studies by James et al. and Stoof et al. found an increased risk of PPH for women receiving prophylaxis compared to women without prophylaxis and a higher PPH risk in both groups compared to healthy women [99,108]. Women who receive prophylactic treatment are at risk for bleeding complications a priori (confounding by indication). Still, current prophylactic treatment doesn't seem to reduce their PPH risk sufficiently. The pooled results from individual case descriptions appear to find the opposite: a decrease in PPH when prophylaxis has been administered. Selection of patients within smaller studies was often unclear; whether cases of interest or a representative view of the population was provided is hard to distinguish. However, most of the data highlights the fact that bleeding complications are encountered, indicating that prophylactic treatment should be optimized in the future. Close monitoring is warranted. Only the retrospective French study by Xu et al. reported a surprisingly low PPH, comparable to the PPH incidence seen in healthy women in France, with no apparent reason [111]. Identical definitions for PPH and individualized care guidelines are adhered (cut off value of 50 IU/dL for prophylactic treatment) to as in Stoof et al., but no information on the method of blood loss estimation was provided.

For VWD type 1, half of the women (51/103) did not receive prophylactic treatment during delivery due to 'normalization' of their clotting factor levels, yet in these women the PPH incidence was still higher than in the general population [18], suggesting that some of these women could have benefited from prophylactic treatment. However, for those women who did receive prophylactic treatment, the PPH incidence was still high; indicating that duration of clotting factor treatment was too short and/or current doses of clotting factor concentrates too low. The higher PPH incidence in women with CS can be explained by the fact that these women represent a high risk group as (emergency) CS are prone to more blood loss than vaginal deliveries (Fig. 2). Studies from deliveries in the general population suggested the beneficial effect of adding antifibrinolytics to prevent or limit PPH [12,112]. The studies in this review are unclear on (frequency of) the use of tranexamic acid to prevent primary PPH, leaving room for improvement.

The included studies provide insight in the heterogeneity of the deliveries from hematologic and obstetrical point of view. Obstetrical diversity within the included population is evident as common risk factors for PPH such as uterus atony, prolonged labor and retained placenta were mentioned in PPH cases [19]. Also, the invasive nature of assisted deliveries and CS are known to increase the risk of excessive bleeding and were described in some cases [19]. Distinguishing between outcomes related to underlying bleeding disorders or the obstetrical component is problematic. Peripartum care combines careful hematologic preparation and close monitoring plus fast response when PPH is impending.

Preconceptional counselling and third trimester clotting factor monitoring aid in creating a complete delivery plan in time relevant for all

involved healthcare workers. Recommendations in current guidelines are based on expert opinion. The majority of studies mention the cut-off values of 50% [27,42,43,48,52,57,58,72,77,85,88,93,101,105,108]. Following this overall cut-off value of 50 IU/dL resulted in a similar incidence of PPH in the prophylactic and non-prophylactic treated women. This warrants a closer look at current guidelines and raises the question whether increasing cut-off values may lower this risk.

This is the first systematic review utilizing an extensive search for studies in multiple electronic databases. 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. Estimated peripartum blood loss is a subjective parameter and gravimetric assessment of blood loss is more reliable but this was not reported [113]. Data mainly originated from case reports, case series and small retrospective cohorts. These study designs are prone to publication bias. Even larger studies generally did not describe their methods in detail. Due to the methods, several studies were excluded: data presented was combined with data on women who were diagnosed after childbirth, data from abortions and the management strategy was entirely unclear [114–117].

5. Conclusion

This systematic review identified 87 studies on a total of 811 deliveries by women with VWD. The available evidence on the peripartum management and associated outcome of these women mostly originates from case series and is of low quality. However, the ongoing high risk for these women to experience PPH is evident: both women with VWD receiving prophylaxis during childbirth and untreated women are at a higher risk of primary and secondary PPH compared to the general population. This review thus highlights the need for better quality evidence from larger prospective cohort studies to improve management strategies and lower the peripartum bleeding risk.

6. Future considerations

Since current prophylactic treatment does not seem to protect women with VWD 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 trough and/or peak levels of FVIII and VWF during and after delivery, considering the fact that these levels are much higher physiologically at time of delivery in healthy women [118]. Furthermore, more aggressive obstetric management, such as obligatory use of uterotonic agents during the 3th stage of labor could be required [119]. Finally, liberal use of tranexamic acid to prevent primary as well as secondary PPH is likely to be helpful [105,112]. We are currently conducting a prospective observational study on pregnancy outcomes in VWD with a higher aimed VWF peak level of 150 IU/dL at delivery and mandatory use of tranexamic acid next to the standard use of uterotonics that will hopefully shed more light on these issues in the near future (PRIDES study, Dutch trial registry number NL6770).

Research agenda

This review highlights the need for more data on the management and outcome of deliveries in women with VWD to prevent bleeding complications. Larger prospective studies are needed to acquire more knowledge on how to optimally prepare these women for childbirth. Selection bias should be avoided to be able to thoroughly investigate the associated risks (for example hyponatremia due to DDAVP use, thrombosis after tranexamic acid or clotting factor concentrate prescription) and outcome of different management options. From our review, the difficulty in designing large high quality studies is evident: many have attempted to collect solid evidence on smaller groups of women while others have reached larger numbers but miss out on

details. National – and potentially international collaboration- is needed in order to collect sufficient evidence on available management strategies. Only then, guidelines can be updated accordingly to lower the peripartum bleeding risk.

Practice points

- Close obstetric monitoring is warranted due to the high risk for developing PPH.
- Current prophylactic treatment is probably insufficiently effective to prevent PPH, suggesting that more women with VWD could benefit from preventive treatment with clotting factor concentrates or DDAVP and tranexamic acid.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.blre.2019.100633>.

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