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ORIGINAL ARTICLE

Desmopressin to prevent and treat bleeding in pregnant women with an inherited bleeding disorder: a systematic literature review

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Abstract

Background: Although desmopressin (DDAVP) is an accessible and inexpensive hemostatic drug, its use in pregnancy is still debated due to safety uncertainties.

Objectives: We aimed to review the safety and effectiveness of DDAVP in women with an inherited bleeding disorder during pregnancy and delivery.

Methods: Databases were searched for articles up to July 25, 2022, reporting maternal and/or neonatal outcomes. PRISMA methodology for systematic reviews and meta-analyses was followed (PROSPERO CRD42022316490).

Results: Fifty-three studies were included, comprising 273 pregnancies. Regarding maternal outcomes, DDAVP was administered in 73 women during pregnancy and in 232 during delivery. Safety outcome was reported in 245 pregnancies, with severe adverse events reported in 2 (1%, hyponatremia with neurologic symptoms). Overall, DDAVP was used as monotherapy in 234 pregnancies, with effectiveness reported in 153 pregnancies (82% effective; 18% ineffective). Regarding neonatal outcomes, out of 60 pregnancies with reported neonatal outcomes after DDAVP use during pregnancy, 2 children (3%) had a severe adverse event (preterm delivery n = 1; fetal growth restriction n = 1). Of the 232 deliveries, 169 neonates were exposed to DDAVP during delivery, and in 114 neonates, safety outcome was reported. Two children (2%) experienced a moderate adverse event (low Apgar score n = 1; transient hyperbilirubinemia not associated with DDAVP n = 1).

Conclusion: DDAVP use during pregnancy and delivery seems safe for the mother, with special attention to the occurrence of hyponatremia and for the child, especially during delivery. However, due to poor study designs and limited documentation of outcomes, a well-designed prospective study is warranted.

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KEYWORDS
blood coagulation disorders, inherited, desmopressin, outcomes, maternal, outcomes, neonatal, pregnancy, review, systematic

1 | INTRODUCTION

Desmopressin, 1-8-deamino-D-arginine vasopressin (DDAVP), a synthetic analog of the antidiuretic hormone vasopressin, is an effective hemostatic drug that increases endogenous von Willebrand factor (VWF) and factor VIII plasma concentrations by stimulating the release of VWF/FVIII stores from vascular endothelial cells [1]. Desmopressin increases circulating VWF and FVIII levels 3- to 5-fold above basal levels, with a plasma half-life of 5 to 8 hours and 8 to 10 hours for FVIII and VWF, respectively [2]. Due to interindividual variability in DDAVP response, a DDAVP test is warranted [3]. Desmopressin is regularly used in patients with inherited bleeding disorders, including von Willebrand disease (VWD), mild to moderate hemophilia A, and platelet function disorders (PFDs), or patients with a bleeding disorder of unknown cause to prevent and treat bleeding [4]. But it can also be used in other less common disorders with hemostatic defects, such as FXI deficiency, Hermansky-Pudlak syndrome (HPS), and Ehlers-Danlos syndrome (EDS) [5]. The common applied dose is 0.3 μ g/kg intravenously or subcutaneously, and this can be capped when body weight exceeds 100 kg with a maximum recommended dose of 30 mcg [6]. Intranasal administration of DDAVP is often used for milder bleeds in the home setting. Repeated administration of DDAVP is limited due to depletion of VWF/FVIII stores, also described as tachyphylaxis [4]. Potential adverse effects of DDAVP are well characterized, compromising mild vasomotor effects (facial flushing, hypotension, and tachycardia), incidental antidiuretic effects (volume overload and hyponatremia with risk of seizures), and rare thrombotic complications (myocardial infarction and stroke). Fluid restriction can help avoid the antidiuretic effects. DDAVP is contradicted in patients with preexisting cardiovascular disease.

Pregnancy and delivery represent a major hemostatic challenge in women with an inherited bleeding disorder. Prophylaxis or treatment of postpartum hemorrhage (PPH) might be required for these patients. In addition, hemostatic treatment may be necessary during pregnancy to prevent bleeding during pregnancy-related procedures (ie, chorionic villus sampling, amniocentesis, cervical cerclage, or pregnancy termination) or other medical interventions. Although DDAVP is effective in patients with an adequate response during DDAVP testing, its utilization during pregnancy and delivery is still debated due to safety concerns for the pregnant woman and her unborn child. DDAVP was initially used during pregnancy in women with diabetes insipidus because of its antidiuretic effects [7]. A review by Ray et al. [7] evaluated DDAVP treatment in pregnant women with diabetes insipidus and reported 53 cases, which are described in 20 publications. In these cases, DDAVP administration during pregnancy did not result in any DDAVP-related maternal or neonatal adverse events. However, there are several important differences in DDAVP use between inherited bleeding disorders and diabetes insipidus. In diabetes insipidus, DDAVP is administered daily and usually orally or intranasally at lower doses (3-40 times lower doses per day in case of intranasal administration). Trigg et al. [8] conducted the first literature review on DDAVP in bleeding disorders and reported 212 pregnancies from a total of 30 publications. Twenty-nine studies reported no significant maternal and neonatal adverse events. One study reported a case of water intoxication seizure and 1 case of preterm labor after DDAVP infusion. No data were provided on the implementation of the fluid restriction regime or risk factors for these 2 complications.

Essentials

- Desmopressin (DDAVP) use in pregnancy is still debated due to safety concerns.
- This systematic review assessed maternal and neonatal outcomes after DDAVP use in pregnancy.
- DDAVP use seems effective and safe in pregnant women, with attention to hyponatremia occurrence.
- DDAVP exposure during pregnancy seems safe for the child, especially during delivery.

Despite the report of only 1 maternal and neonatal adverse event and limited information regarding potential contributing factors, such as the implementation of fluid intake restriction and the presence of other relevant conditions, safety concerns are still predominant in daily practice. This leads to an overall avoidance of DDAVP treatment during pregnancy and delivery. Therefore, additional data on safety are required. Moreover, evidence regarding effectiveness is also needed, as bleeding during pregnancy and delivery, especially PPH, leads to high morbidity and mortality rates [9]. Consequently, this systematic review aimed to evaluate the safety and effectiveness of DDAVP during pregnancy, delivery, and the postpartum period in women with an inherited bleeding disorder.

2 | METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology for systematic reviews and meta-analysis and registered at PROSPERO, an international prospective register of systematic reviews (registration number CRD42022316490) [10].

2.1 | Search strategy

A medical research library specialist codesigned and conducted the research strategy. The search was performed in EMBASE, Medline ALL, Cochrane Central Register of Controlled Trials, Web of Science Core Collection, and Google Scholar. All databases were searched from inception until July 25, 2022. The search strategy included multiple medical heading terms and keywords for inherited bleeding disorders, desmopressin, and pregnancy. The full details of the literature research, including used key terms, are available in the supplementary material (Supplementary Text S1).

2.2 | Study selection and eligibility criteria

Retrieved citations were independently assessed by 2 reviewers (W.A. and L.G.R.R.) to identify studies that met the inclusion criteria. Disagreements were discussed until a consensus was reached. English articles reporting maternal and/or neonatal outcomes during DDAVP treatment in pregnant women with an inherited bleeding disorder were included. Besides VWD, hemophilia carriership, PFD, and rare diseases such as FXI deficiency, EDS, HPS, and Noonan syndrome were selected. DDAVP use in pregnancy was evaluated from reports if treatment was received during the first, second, and third trimester (antepartum); during delivery (intrapartum); and in the postpartum period (defined as until 6 weeks after child delivery). For articles published more than once and suspected of overlapping study populations, only the study with the largest number of pregnancies and most complete data were included. All review articles were screened to select case reports. Conference abstracts and articles concerning acquired bleeding disorders or articles missing any outcomes related to DDAVP use were excluded. The reference lists of included studies identified by the literature search were also cross-checked for relevant citations.

2.3 | Data extraction and assessment

For each included study, the following information was collected: study design, study population, treatment indication, details of DDAVP administration (route, dosage, and frequency), additional hemostatic treatment such as antifibrinolytic agents, factor concentrates, cryoprecipitate, platelet concentrates or other blood products, mode of delivery, and maternal and neonatal outcomes. Maternal outcomes included the effectiveness of DDAVP treatment to prevent or treat bleeding. DDAVP was considered effective if there was minimal bleeding, including PPH, or bleeding was resolved after DDAVP and no additional hemostatic agents were required. PPH was defined, according to the World Health Organization definition, as a blood loss of ≥500 mL within 24 hours after delivery, and for cesarean section, a blood loss of ≥1000 mL according to the commonly used definition [11,12]. Only DDAVP treatment without additional replacement therapies with factor concentrates or cryoprecipitate was evaluated for effectiveness. For safety evaluation, reported adverse events occurring in both mother and child were collected, with special attention to adverse effects related to DDAVP comprising vasomotor effects, antidiuretic effects, and thrombotic complications [4]. For the child, adverse events were categorized into adverse events following (1) DDAVP exposure during pregnancy (antepartum exposure) and (2) DDAVP exposure during delivery (intrapartum exposure). Adverse events were graded according to severity (mild, moderate, severe, and life-threatening) using the Common Terminology Criteria for Adverse Events. Data on maternal and neonatal outcomes were defined as unknown if studies did not mention the outcome or authors reported outcomes as unknown.

Two reviewers (W.A. and L.G.R.R.) independently extracted the data from each included study using a standardized data collection form. Discrepancies were resolved by consensus after a mutual discussion. Due to the methodological heterogeneity of the studies, a descriptive review of all included studies was performed with a summary of outcomes rather than a statistical analysis.

2.4 | Risk of bias assessment

The risk of bias was assessed according to the National Institutes of Health quality assessment tool for observational and cross-sectional studies [13]. Two reviewers (W.A. and L.G.R.R.) independently assessed and rated each observational study. Quality rating conforming to the tool (good, fair, or poor) was used to assess the certainty of evidence. Inconsistencies were discussed and resolved by consensus. Studies were not excluded based on risk of bias assessment. The design of case reports was considered a bias; therefore, case reports were not assessed.

3 | RESULTS

3.1 | Data retrieval

The systematic review yielded a total of 1029 unique references that were screened using predetermined criteria. A total of 53 unique articles met the inclusion criteria. The flow chart (Figure 1) shows the article selection process from the initial search to the final inclusion or exclusion.

3.2 | Study characteristics

All studies were published between 1986 and 2022 (Figure 2). Twenty-one articles were observational studies (prospective n = 10; retrospective n = 11) [14–34]. The remaining 32 articles were case reports or case series [35–66]. Observational studies were conducted in the United States (n = 6) and Italy (n = 6), followed by the United Kingdom (n = 3) and other European or Asian countries (n = 6). Case reports were conducted in different countries around the

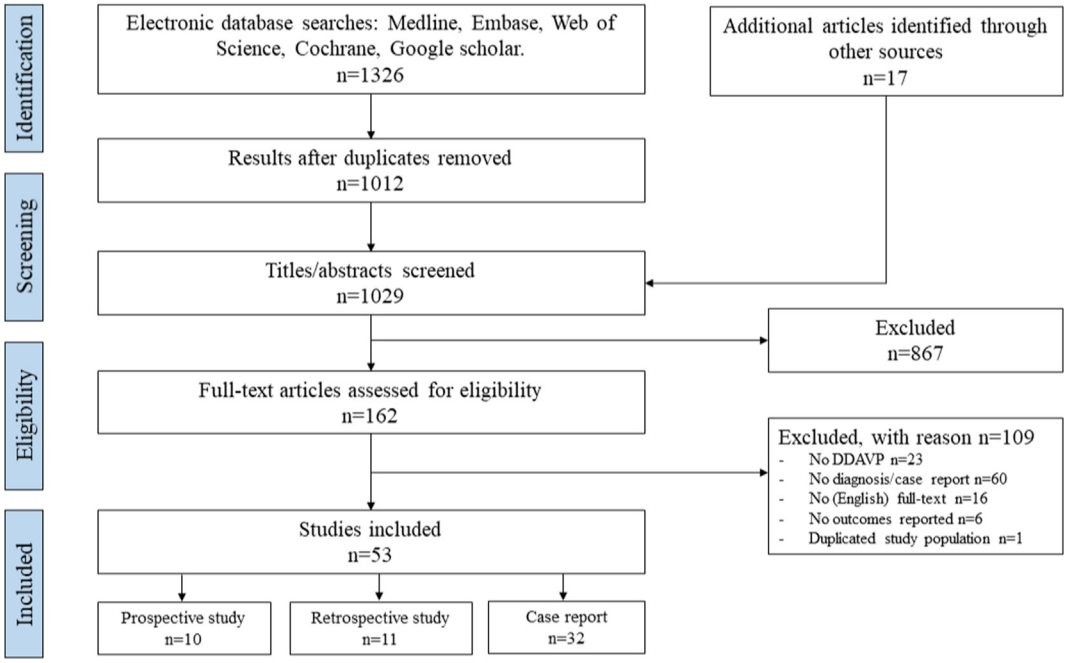

FIGURE 1 Flow chart for study identification, adapted from the PRISMA flow diagram. DDAVP, desmopressin; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

world, with the most reports in the United States (*n* = 15). The majority of observational studies focused on VWD (*n* = 17). Other observational studies included patients with hemophilia carriership (*n* = 2), PFD (*n* = 1), and FIX deficiency (*n* = 1). These disorders were also studied in case reports among other rare inherited bleeding disorders, including HPS, EDS, and a combination of bleeding disorders. In 9 included studies, the main objective of the study was to investigate the safety and/or effectiveness of DDAVP in pregnancy (5 observational studies [14,16,26,29,31] and 4 case reports [39,45,61,66]). Other studies mainly focused on the management of pregnancy and delivery and reported the use of DDAVP, among other outcomes. Figure 3 presents the risk of bias assessment. Twelve studies were adjudicated as having poor quality, and 9 had fair quality. The most prevalent limitations were found in items related to sample size justification, reporting exposure and outcome measures, and statistical analyses.

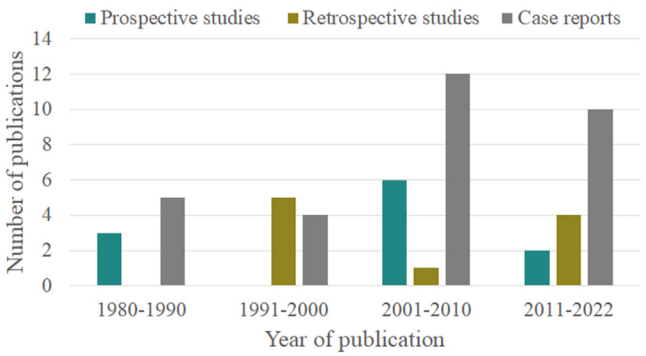

FIGURE 2 Publication year of included studies.

3.3 | Studied pregnancies

A total of 273 pregnancies were studied (237 observational studies; 36 case reports). The exact number of women is unknown, as some studies did not report this information. VWD was most involved with 212 (78%) pregnancies, followed by hemophilia A carriership (31 pregnancies, 11%), PFD (14 pregnancies, 5%), HPS (8 pregnancies, 3%), FXI deficiency (3 pregnancies, 1%), EDS (2 pregnancies, 1%), and a combination of disorders (2 pregnancies, 1%). Regarding the type of disease in VWD, VWD type 1 was observed in 79 pregnancies (37%), VWD type 2 in 4 pregnancies (2%), VWD type 3 in 1 pregnancy, and platelet type VWD in 1 pregnancy. The type of VWD was not specified or reported as unknown in 127 pregnancies. Concerning PFD, patients with various disorders were treated with DDAVP: Gray platelet syndrome (2 pregnancies), Bernard-Soulier syndrome (4 pregnancies), platelet storage pool disorder (5 pregnancies), and Glanzmann's thrombasthenia (1 pregnancy). The type of PFD was not specified in the 2 pregnancies. Of the 273 pregnancies, DDAVP was administered in a total of 311 treatment episodes. This included 235 pregnancies with 1 treatment episode and 38 pregnancies with 2 treatment episodes. Specifically, DDAVP was administrated during pregnancy (antepartum period) in 73 pregnancies, during delivery in 232 pregnancies, and during the postpartum period in 6 pregnancies. During the antepartum period, DDAVP was given in all 3 trimesters (first trimester, 28 [38%] pregnancies; second trimester, 12 [16%] pregnancies; third trimester, 33 pregnancies [45%]). In these cases, the indication for DDAVP was to prevent bleeding (*n* = 71) and to treat (*n* = 2) obstetrical-related bleeding (7 studies [18,20,22,26,29,36,52]). In 232 pregnancies where DDAVP was given during delivery, the indication for DDAVP was PPH

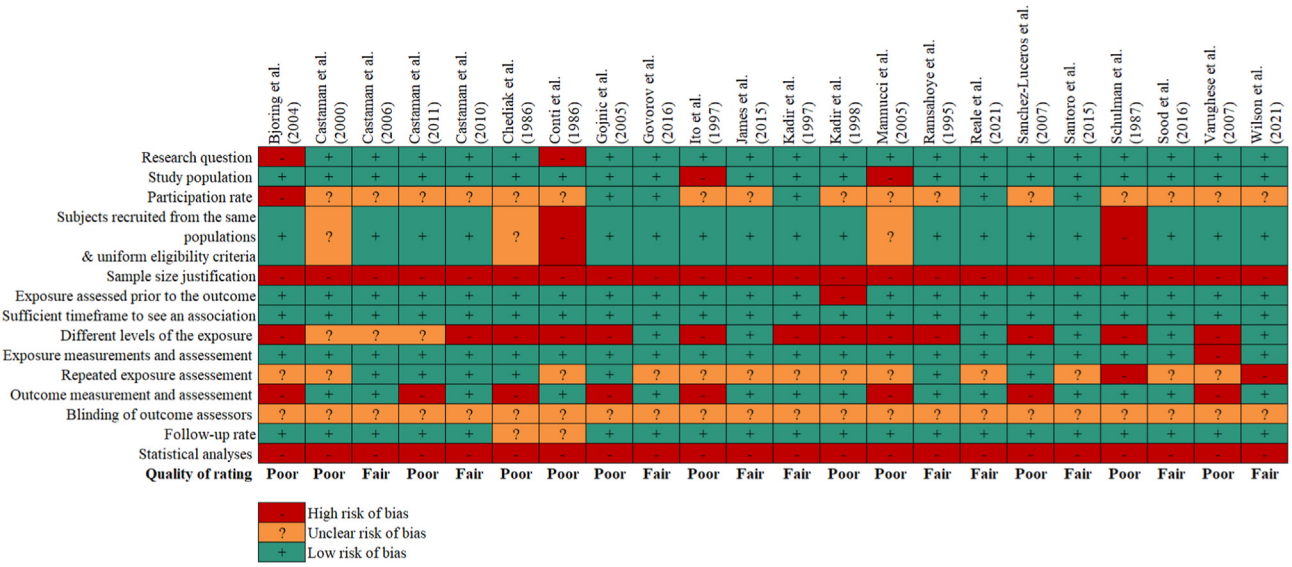

FIGURE 3 Risk of bias assessment using the National Institute of Health quality assessment tool for observational cohort and cross-sectional studies.

prophylaxis (n = 226) and PPH treatment (n = 6) [14–18,20,21,23–25,27–31,33–46,48–51,55,56,58–66]. In addition, in 6 pregnancies, DDAVP was initiated as treatment during the late postpartum period due to obstetrical-related bleeding [19,32,47,53,54,57]. In 38 pregnancies with 2 treatment episodes, DDAVP was given during pregnancy and delivery [20,29,36]. In 32 of these pregnancies, DDVAP was administered from week 36 of gestational age until the postpartum period with an unknown dose frequency [20]. In relation to the use of tranexamic acid during delivery in combination with DDAVP (without replacement therapy), 2 observational studies and 2 case reports documented this combined treatment. This combined treatment approach was applied in 15 pregnancies (12 in VWD and 3 in PFD) as prophylaxis for PPH. Different dosing regimens were applied, commencing with intravenous (i.v.) administration and continuing with oral administration of tranexamic acid for different treatment durations. Concerning the route of administration for each treatment episode, DDAVP was given intravenously in 213 pregnancies (75%), intranasally in 67 pregnancies (24%), and subcutaneously in 2 (1%) pregnancies. The route of administration was unknown in 29 pregnancies. Regarding dose frequency, DDAVP was administered in 1 dose in the majority of cases (n = 152, 75%), followed by 2 doses (n = 32, 15%), and ≥3 doses (n = 19, 9%). In 108 treatment episodes, the dose frequency was not reported. In addition to the recommended dosage for i.v. DDAVP of 0.3 μg/kg, dosages of 0.2 and 0.4 μg/kg were also used.

3.4 | Maternal and neonatal outcomes

Table 1 provides an overview of maternal and neonatal outcomes of included observational studies. Supplementary Text S2 summarizes the outcome of each case report.

3.4.1 | Maternal outcomes: effectiveness

Of the 73 pregnancies in which DDAVP was administered during antepartum, in 41 pregnancies DDAVP was given as monotherapy without replacement therapy. The indication for DDAVP in these pregnancies was prenatal diagnostic testing or other obstetrical-related intervention (planned abortion and cervical cerclage) (n = 38), DDAVP response test (n = 1), and treatment for an obstetrical-related bleeding (retroplacental hematoma and vaginal bleeding) (n = 2). DDAVP was reported to be effective in all pregnancies except in 1 with an unknown outcome. DDAVP was administered intravenously in all cases. Most pregnancies received 1 dose (29 of 41 pregnancies, 70%), and some received 3 or more doses (10 of 41 pregnancies, 24%). In the remaining 32 pregnancies reported in 1 study, DDAVP was indicated for PPH prevention and was initiated during the antepartum period (36 weeks of gestation) with intranasal administration until 6 weeks of the postpartum period. In addition, these women also received treatment with replacement therapy during delivery [20]. During the intrapartum period, DDAVP was administered without additional replacement therapy in 192 out of 232 pregnancies. PPH prophylaxis was the most frequent indication (185 pregnancies, 97%), followed by PPH treatment (6 pregnancies, 3%). The majority of women (165 pregnancies out of 192 pregnancies) had VWD. Moreover, in 87 of these 165 pregnancies, the effectiveness of treatment was reported. The treatment was effective in 74 pregnancies (85%) and ineffective in 13 pregnancies (15%). Table 2 summarizes the effectiveness outcome of each inherited bleeding disorder. Vaginal delivery was the most frequent mode of delivery in pregnancies with DDAVP monotherapy, with 84 (57%) pregnancies, 63 (43%) pregnancies with cesarean section, and in 44 pregnancies the mode of delivery was unknown. Concerning the combined treatment with DDAVP and tranexamic acid in 15 pregnancies for PPH

TABLE 1 An overview of pregnancies, treatment with DDAVP, and maternal and neonatal outcomes of each included observational study.

References (year)/ country	Pregnancies using DDAVP/total pregnancies[a] (*n*/*n*)	Inherited bleeding disorder/type[b]	Indication for DDAVP/timing of dosing (trimester/ delivery/postpartum)	Treatment (route, dosage, dose frequency)	Mode of delivery	Maternal outcomes	Neonatal outcomes
Bjoring et al. [14] *United States*	7/19	VWD - Type NS *n* = 6 - Type 3 *n* = 1	PPH prophylaxis before delivery	DDAVP, 0.3 μg/kg, i.v., 1 dose	VD	- One patient had PPH. This was a patient with type 3 VWD who was responsive to DDAVP. - No adverse effects or complications	No adverse events or effects
Castaman et al. [15] *Italy*	3/6	VWD - Type 1 *n* = 3	PPH prophylaxis, after delivery	DDAVP i.v., 2 doses, dosage not specified	VD	- No Primary PPH - Adverse effects: not mentioned	NA
Castaman et al. [16] *Italy*	5/6	VWD - Type 1/Vicenza *n* = 5	PPH prophylaxis, after delivery	DDAVP, 0.3 μg/kg, i.v., 2 doses every 24 h	VD	- No primary PPH (≤300 mL) - No excessive blood in the late puerperium - Adverse effects: not mentioned	NA
Castaman et al. [17] *Italy*	23/31	VWD - Type 1 *n* = 15 - Type 1/Vicenza *n* = 6 - Type 2 *n* = 2	PPH prophylaxis, after delivery	DDAVP, 0.3 μg/kg, i.v., 1 dose *n* = 5, 2 doses *n* = 13, and 3 doses *n* = 5	VD	- No primary PPH - One patient had secondary PPH on day 5, treated with FVIII and VWF concentrate - Adverse effects: no signs of water intoxication or serum electrolyte abnormalities	NA
Chediak et al. [18] *United States*	2/8	VWD - Patient 1: type 1 - Patient 2: type NS	- Patient 1: PPH prophylaxis, after delivery - Patient 2: a test dose, third trimester	- Patient 1: DDAVP, 0.3 μg/kg, i.v., 3 doses every 18 h, cryoprecipitate - Patient 2: DDAVP, 0.4 μg/kg i.v., 1 dose	Patient 1: CS Patient 2: NS	- PPH occurrence in both patients, not specified - Patient 1: hyponatremia (108 mEq/L), water intoxication seizure - Patient 2: premature labor	- Patient 1: NA - Patient 2: preterm newborn at 36 weeks - No other adverse events or effects
Conti et al. [19] *Italy*	1/5	VWD - Type 1	Secondary PPH treatment, postpartum	- DDAVP, 0.4 μg/kg, i.v., 1 dose; - 4 x Packed cells	CS	- Bleeding stopped after DDAVP administration - Adverse effects: not mentioned	NA
Gojnic et al. [20] *Serbia*	32/32	VWD - Type 1 and type 2A, exact numbers NS	PPH prophylaxis, 36 weeks gestation until 4 wks postpartum	- DDAVP, 300 μg i.n., dose not mentioned - 40-60 IU/kg hemate P; 4 doses every 24 h - cryoprecipitate and fresh frozen plasma, 4-6 doses	VD *n* = 26 CS *n* = 6	- No PPH - No adverse events, including DDAVP-related effects	No intracranial hemorrhage

TABLE 1 (Continued)

References (year)/ country	Pregnancies using DDAVP/total pregnancies[a] (*n*/*n*)	Inherited bleeding disorder/type[b]	Indication for DDAVP/timing of dosing (trimester/ delivery/postpartum)	Treatment (route, dosage, dose frequency)	Mode of delivery	Maternal outcomes	Neonatal outcomes
Govorov et al. [21] *Sweden*	12/59	VWD - Type 1 *n* = 11 - Type 2 *n* = 1	PPH prophylaxis, timing of administration not specified	- DDAVP, 1 dose, further details not specified - Tranexamic acid, i.v. or oral, started from labor and continued every 8 h and continued 2 to 10 d	NS	- Primary PPH *n* = 6, no blood transfusion required - Secondary PPH *n* = 1 - No vaginal hematoma - Adverse effects: not mentioned	Not mentioned Exposure unknown
Ito et al. [22] *Japan*	1/14	VWD - Type 1	Induced abortion, first trimester	DDAVP i.v., dose not specified	NA	- No abnormal bleeding - No complications	NA
James et al. [23] *United States*	2/35	VWD - Type 1	PPH prophylaxis before delivery	- DDAVP, 1 dose, dosage and route not specified - VWF concentrate, 1 dose *n* = 1, 2 doses *n* = 1	NS	- Primary PPH not specified - No excessive blood loss until 6 weeks postpartum - Adverse effects: not mentioned	Not mentioned
Kadir et al. [24] *United Kingdom*	4/82	HA-carriership	- PPH prophylaxis, after delivery *n* = 3 - Primary PPH treatment *n* = 1	DDAVP i.v., 1 dose, dosage not specified	VD *n* = 1 NS *n* = 3	- No primary PPH in 3 patients with prophylaxis - After DDAVP, bleeding was controlled in the patient with primary PPH - Adverse effects: not mentioned	NA
Kadir et al. [25] *United Kingdom*	1/112	VWD - Type NS	Treatment primary PPH, after delivery	DDAVP i.v., dose and dosage not specified	VD	- Not mentioned if the bleeding was controlled - Adverse effects: not mentioned	NA
Mannucci [26] *Italy*	32/32	VWD *n* = 5 - Type 1 HA-carrier *n* = 27	- Chorionic villus sampling, first trimester *n* = 20 - Amniocentesis, second trimester *n* = 12 - Planned abortion *n* = 12	- DDAVP, 0.3 μg/kg, i.v., 1 dose *n* = 22 and 3-4 doses *n* = 10, additional dose for planned abortion *n* = 12	NA	- No abnormal bleeding *n* = 32 - Only headache and mild facial flushing were reported (*n* = 1 to *n* = 32, not specified) - No clinical signs of water intoxication or significant increase in body weight	Healthy newborns *n* = 20
Ramsahoye et al. [27] *United Kingdom*	1/24	VWD - Type 1	PPH prophylaxis, after delivery	DDAVP, 0.4 μg/kg, i.v., 3 doses	CS	- No primary or secondary PPH - No complications or adverse effects	NA
Reale et al. [28] *United States*	24/106	VWD - Type 1 *n* = 20 - Type unknown *n* = 4	PPH prophylaxis, before delivery *n* = 24	DDAVP, 0.3 μg/kg, i.v., dose not specified	NS	- Three patients had primary PPH (>1000 mL); 1 of these received a second DDAVP dose to treat PPH - No neuraxial hematoma or thromboembolic events - Other adverse effects not mentioned	Not mentioned

(Continues)

TABLE 1 (Continued)

References (year)/ country	Pregnancies using DDAVP/total pregnancies[a] (*n*/*n*)	Inherited bleeding disorder/type[b]	Indication for DDAVP/timing of dosing (trimester/ delivery/postpartum)	Treatment (route, dosage, dose frequency)	Mode of delivery	Maternal outcomes	Neonatal outcomes
Sanchez et al. [29] *Argentina*	75/75	VWD - Type NS	- Retroplacental haematoma, first trimester *n* = 1 - Cervical cerclage, first trimester *n* = 4 - PPH prophylaxis, before delivery *n* = 75	DDAVP, 0.3 μg/kg, i.v., - First trimester: 2 doses *n* = 1, 1 dose *n* = 4 - Before delivery: 1 dose *n* = 75	VD, *n* = 30; CS, *n* = 45	- First trimester: no bleeding reported, no increased uterine tone, or water intoxication - Delivery: postpartum hemorrhage not specified No hyponatremia or thromboembolic events No other adverse effects were reported	- First trimester: healthy newborn - Before delivery: no premature newborns, no neonatal bleeding, average weight reported *n* = *63*
Santoro et al. [30] Italy	3/9	FXI deficiency	PPH prophylaxis during CS	DDAVP, 0.3 μg/kg, dose and route not specified	CS	- No PPH - One patient with hyponatremia and transitory neurologic complications	Not mentioned Exposure unknown
Schulman et al. [31] *Sweden*	1/1	PFD	PPH prophylaxis, after delivery	- DDAVP, 0.2 μg/kg, i.v., dose not mentioned - Tranexamic acid	NS	- No hemorrhagic complication - Adverse effects: not mentioned	NA
Sood et al. [32] *United States*	1/12	VWD - Type 1	Secondary PPH treatment, postpartum	DDAVP, intranasal. Dose and frequency not mentioned		- Self-administration at home - Adverse effects: not mentioned	NA
Varughese & Cohen [33] *United States*	2/64	VWD - Type 1	PPH prophylaxis after delivery	DDAVP, further details not specified	VD	- No primary PPH - Adverse effects: not mentioned	NA
Wilson et al. [34] *Australia*	6/23	VWD - Type 1 - Type 2, exact numbers NS	- PPH prophylaxis, after delivery *n* = 4 - Treatment of primary PPH *n* = 2	- DDAVP i.v., dose not specified *n* = 6 - Tranexamic acid for 5 d and Biostate, 1 dose (*n* =1 with PPH prophylaxis)	VD *n* = 2 NS *n* = 4	- PPH prophylaxis: 1 patient developed primary PPH, treated with Biostate and blood transfusion - PPH treatment: not mentioned if bleeding was controlled - Adverse effects: not mentioned reported	NA

Not mentioned: authors did not report or define any outcome. If NS was added in the outcomes columns, it indicates that the authors reported one or more outcomes, but they did not provide any specific details about those outcomes.

CS, cesarean section; DDAVP, desmopressin; FIX deficiency, factor IX deficiency; HA-carriership, hemophilia A carriership; i.n. intranasal; i.v. intravenous; PFD inherited platelet function disorder; NA, not applicable; NS, not specified; PPH, postpartum hemorrhage; VD, vaginal delivery; VWD, Von Willebrand disease.

[a] Total pregnancies: number of pregnancies with or without DDAVP treatment.

[b] Only the type of disease reported by the authors is added.

TABLE 2 Effectiveness outcome of desmopressin monotherapy during intrapartum period.

Inherited bleeding disorder	Total Pregnancies, *n*	Unknown Pregnancies, *n*	Effective Pregnancies, *n* (%)[a]	Ineffective Pregnancies, *n* (%)[a]
VWD	165	78	74 (85)	13 (15)
Hemophilia A carriership	4	0	4 (100)	0
PFD	8	0	6 (75)	2 (25)
FXI deficiency	3	0	3 (100)	0
HPS	8	0	4 (50)	4 (50)
ESD	2	0	1 (50)	1 (50)
Combined bleeding disorder	2	1	1 (100)	0
Total	192	79	93	20

Effective: studies reported "no postpartum hemorrhage" or blood loss ≤ 500 mL.

Ineffective: studies reported "postpartum hemorrhage" or a blood loss ≥ 500 mL, and in case cesarean section ≥ 1000 mL or additional unplanned hemostatic agents or blood products were needed.

Unknown: studies did not mention effectiveness outcomes or reported "unknown.

ESD, Ehlers-Danlos syndrome; FXI deficiency, factor XI deficiency; HPS, Hermansky-Pudlak syndrome; PFD, platelet function disorder; VWD, Von Willebrand disease.

[a] The percentages are derived from known outcomes.

prophylaxis, PPH was reported in 7 of these pregnancies and no PPH in 8 pregnancies.

In 6 pregnancies in which DDAVP was administrated in the late postpartum period to treat obstetrical-related complications (secondary PPH and treatment of superficial wound), the treatment was effective in all cases.

3.4.2 | Maternal outcomes: safety

In one observational study, it was reported that mild adverse events such as facial flushing and headache occurred in 1 to 32 pregnancies without further details [26]. In addition, 1 case report also described mild adverse events such as facial flushing in 1 pregnancy [48]. Two observational studies reported a severe adverse event in 2 (1%) pregnancies. One pregnancy was given DDAVP immediately after cesarean section for PPH prophylaxis [18]. A total of 3 doses were given every 18 hours and intravenously administered in a dosage of 0.3 μg/kg. Afterward, the patient developed a water intoxication seizure with hyponatremia (sodium plasma level, 108 mEq/L). Other details were not provided. The second patient received DDAVP during cesarean section for PPH prophylaxis [30]. One dose of 0.3 μg/kg was given. Afterward, the patient developed transient neurologic symptoms; further details were not specified. In both cases, no information was available regarding the application of water restriction therapy and the monitoring during and after DDAVP administration. In 66 (21%) pregnancies, no information on safety outcomes was reported.

3.4.3 | Neonatal outcomes

Of the 73 pregnancies with DDAVP during pregnancy, 60 resulted in the birth of a child. In 1 pregnancy, DDAVP was indicated to prevent bleeding before a planned abortion [22]. In addition, in a single study, DDAVP was given to 12 pregnancies prior to undergoing prenatal diagnostic testing and eventually for subsequent planned abortion [26]. Two severe adverse events were reported. Due to preterm labor, 1 neonate was born at 36 weeks of gestation [18]. In this case, the pregnant woman received 1 dose of DDAVP (0.3 μg/kg, intravenously) at 36 weeks of gestation for a DDAVP test, and the authors mentioned that preterm labor was related to DDAVP administration. Besides the preterm labor, no other adverse events were mentioned, and no further details were provided. The second neonate with severe adverse events was born with fetal growth restriction at 36 weeks of gestation [52]. In this case, the women received DDAVP in the first trimester (route and dosage not specified) before amniocentesis. The authors linked preterm labor to the presence of insulin-dependent diabetes in pregnant women.

Of the 232 deliveries, 169 neonates were exposed to DDAVP during delivery (unknown exposure, 7 deliveries), ie, DDAVP was given to the women before the umbilical cord was clamped. Two (1%) neonates experienced a moderate adverse event. The first neonate had a low Apgar score and was admitted for 1 day in the intensive care for observation. In this case, the women received 0.3 ug/kg DDAVP intravenously, 2 doses every 12 hours for PPH prophylaxis. The second neonate had transient hyperbilirubinemia and received phototherapy [51]. DDAVP was intravenously administered for PPH prophylaxis with an unknown dosage and route. In 55 (33%) deliveries, no neonatal outcomes were mentioned. Table 3 summarizes the maternal and neonatal safety outcomes. Thirty-eight neonates were exposed to DDAVP twice, both during pregnancy and delivery [20,29,36]. Among them, 37 neonates had no adverse events, while the safety outcome for 1 neonate was not reported (unknown).

Finally, 3 adverse events were reported (1 maternal and 2 neonatal adverse events) that were not correlated to DDAVP administration and/or had clearly other cause(s) (Supplementary Text S3).

TABLE 3 Safety outcomes after desmopressin administration during pregnancy and delivery.

Maternal outcomes - AE	
Antepartum and intrapartum/postpartum	**Pregnancies, *n* (%)[a]**
No AE	210 (86)
Mild AE	2-33 (1-13)[b]
Severe AE	2 (1)
Unknown	66
Total[c]	311
Neonatal outcomes - AE	
Antepartum exposure	**Pregnancies, *n* (%)[a]**
No AE	58 (97)
Mild AE	0
Moderate AE	0
Severe AE	2 (3)
Unknown	0
Not applicable[d]	13
Total	73
Intrapartum exposure	**Deliveries, *n* (%)[a]**
No AE	112 (98)
Mild AE	0
Moderate AE	2 (2)
Severe AE	0
Unknown	55
Total[e]	169

No AE: studies explicitly mentioned "no AE" or "no complications" or denied any specific AE.

Unknown: studies did not mention safety outcomes or reported them as "unknown.

Adverse events severity is graded according to Common Terminology Criteria for Adverse Events.

AE, adverse event.

[a] The percentages shown are derived from known outcomes.

[b] One study reported that 1 to 32 pregnancies experienced mild adverse events with no further details, and 1 case reported 1 mild adverse event.

[c] Total treatment episodes with DDAVP treatment during pregnancy (73 pregnancies), delivery (232 pregnancies), and the postpartum period (6 pregnancies).

[d] In 12 pregnancies, DDAVP was given for prenatal testing with a subsequently planned pregnancy abortion. In 1 pregnancy, DDAVP was given for a planned abortion.

[e] Total neonates from each delivery: 1 delivery resulted in 3 neonates.

4 | DISCUSSION

The aim of this systematic review was to review the safety and effectiveness of DDAVP during pregnancy, the intrapartum, and the postpartum period in women with an inherited bleeding disorder. DDAVP is an important choice of treatment in most patients with inherited bleeding disorders. Despite its advantages, such as easy accessibility, low costs, and patient-friendly intranasal administration, there are concerns regarding its safety for pregnant women and their children that require exploration. Furthermore, there is a need for effective data concerning bleeding during pregnancy and delivery, especially PPH, which has high morbidity and mortality rates. This systematic review provides a comprehensive summary of the available evidence regarding these concerns.

According to the findings of this review, monotherapy with DDAVP was effective in treating and preventing bleeding, especially in VWD. Seven studies reported DDAVP use during pregnancy for prenatal diagnostic testing but also for termination of pregnancy. No adverse bleeding events were reported in these pregnancies. In the majority of pregnancies, DDAVP was used during the intrapartum period and was indicated for PPH prophylaxis. In VWD, high effectiveness was reported for DDAVP monotherapy. However, the large amount of missing outcome data presents a challenge for drawing definitive conclusions. In other inherited bleeding disorders, only small numbers of pregnancies were reported with limited effectiveness, especially pregnancies with PFD and HPS. Therefore, these results should be interpreted with caution. DDAVP was mainly administered intravenously with 1 dose, but 5 included studies also reported the use of intranasal administration. Studies have shown that intranasal administration provides an equivalent improvement in hemostasis as 0.2 μg/kg i.v. DDAVP. Therefore, intranasal administration may not have a negative impact on effectiveness [67,68]. With respect to the combined treatment involving DDAVP and tranexamic acid, our review has identified a limited number of pregnancies that were treated with this combination. Consequently, drawing any conclusions about its effectiveness is not possible. However, guidelines recommend the use of tranexamic acid in combination with DDAVP or replacement therapy during delivery and postpartum period [3].

Severe adverse maternal outcomes after DDAVP administration were uncommon. Of the included 273 pregnancies with DDAVP administration, 2 pregnancies were accompanied by severe adverse events. One pregnancy was complicated by a water intoxication seizure due to severe hyponatremia, and the second pregnancy by transient neurologic symptoms; both women had a cesarean section. Antidiuretic effects of DDAVP are a common concern; therefore, a recommended fluid restriction after administration is applied for all patients [3]. Pregnant women might be at higher risk due to commonly used i.v. fluids, especially in those with a cesarean section, and the physiological changes during pregnancy may aggravate water retention and changes in the pharmacokinetics of DDAVP [69]. In addition, the use of oxytocin is common during delivery, which may also contribute to hyponatremia [70]. In the majority of reviewed studies, there was a lack of information regarding the implementation of fluid restriction and monitoring measures. However, by incorporating fluid restriction, closely monitoring patients, and measuring sodium levels, it is possible to avoid these severe complications. In addition, an important question is whether the frequency of DDAVP administration is associated with maternal safety. Our review reveals that different dose frequencies were used, with a single DDAVP dose in the majority of pregnancies (75%). However, as different dose

frequencies were applied in pregnancies where maternal adverse events occurred and data on both dose frequency and outcome were missing, drawing conclusions about the association between dose frequency and adverse events is not possible.

Regarding neonatal outcomes, current data suggest that the use of DDAVP is generally safe for children, especially when administered during delivery. During intrapartum DDAVP, 2 (2%) moderate adverse events were reported, with 1 neonate presenting with a lower Apgar score without consequences and the other neonate with transient hyperbilirubinemia. The latter adverse event is not associated with DDAVP. On the other hand, DDAVP administration during the antepartum period resulted in 2 (3%) neonatal adverse events, specifically preterm labor and fetal growth restriction. The incidence of preterm labor is approximately 10% in the general population [71]. Theoretically, DDAVP could lead to uterine contraction due to binding to the oxytocin receptor [72], while intrauterine growth restriction could be the consequence of poor placental flow due to the vasopressor effect of DDAVP. Nonetheless, due to the absence of information regarding other potential risk factors or causes that could contribute to these severe adverse events, it remains challenging to establish a direct causal relationship or association between DDAVP and these events. Moreover, *in vitro* models of placentae showed that DDAVP crosses the placenta but leads to minimal detectable concentrations [73]. Similar to data from DDAVP use in pregnant women with diabetes insipidus, no teratogenic effects in fetuses were reported [7]. It is important to note that more data are available on the use of DDAVP during delivery (114 deliveries with reported neonatal outcomes) compared with the antepartum period (60 pregnancies with reported neonatal outcomes). In relation to the dose frequency and neonatal safety, our review reveals that neonatal adverse events occurred in patients with different dose frequencies. Due to missing data on dose frequency and outcomes in studies, conclusions regarding the association between dose frequency and neonatal adverse events cannot be drawn.

Our systematic review contains additional evidence on the safety outcomes. Compared with the review by Trigg et al. [8], this review included 23 additional studies and 57 pregnancies. Regarding the safety outcomes, 1 severe maternal adverse event and 1 severe and 1 moderate neonatal adverse event were added.

This review has several limitations. First, the fact that only a few studies aimed to investigate the effectiveness and safety of DDAVP indicates that the remaining studies may have incomplete results on these outcomes. Second, due to heterogeneity in the included study population with lack of information about data that affect the effectiveness outcome, conclusions regarding effectiveness are difficult to draw. Thirdly, case reports were included, which may have contributed to biased results on outcomes, especially effectiveness outcomes. However, case reports are useful regarding safety, and they describe adverse events that remain unnoticed in observational studies or clinical trials. Finally, the majority of studies were poorly designed, potentially generating unreliable and/or biased results.

In conclusion, our review provides updated evidence on the effectiveness and safety outcome of DDAVP use during pregnancy and delivery in women with an inherited bleeding disorder. Based on current data, DDAVP use during pregnancy and delivery seems safe for the mother, with special attention to the occurrence of hyponatremia and for the child, especially during delivery. However, due to poor study designs and limited documentation of outcomes, a well-designed prospective study is still warranted.

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AUTHOR CONTRIBUTIONS

W.A. designed the study and conducted the search strategy. W.A. and L.G.R.R. screened studies for eligibility and completed the data extraction. W.A. and L.G.R.R. assessed the risk of bias. W.A. and L.G.R.R. interpreted and analyzed data. W.A. wrote the manuscript. L.G.R.R, F.W.G.L., M.J.H.A.K., K.P.M.G., O.T., R.A.K., and M.H.C. critically revised the manuscript. M.H.C supervised the study. All authors read and approved the final manuscript.

DECLARATION OF COMPETING INTERESTS

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SUPPLEMENTARY MATERIAL

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