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BRIEF REPORT

Hemostatic management of von Willebrand disease during childbirth with a plasma-derived von Willebrand factor/factor VIII concentrate

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Abstract

Background: Females with von Willebrand disease (VWD) do not show the same increases in von Willebrand factor and factor (F)VIII levels during pregnancy as females without VWD and are at higher risk of excessive bleeding associated with childbirth. Data on hemostatic management for childbirth in VWD patients are limited.

Objectives: To evaluate the dosing, efficacy, and safety of plasma-derived von Willebrand factor/FVIII (wilate) for prevention of excessive bleeding associated with childbirth in females with any type of VWD.

Methods: Data for females with VWD who received wilate for hemostatic coverage for childbirth during 2 prospective clinical studies were analyzed.

Results: Ten females with VWD and a mean age at enrolment of 29.6 years were treated with wilate to prevent excessive bleeding associated with childbirth. Two patients had type 1, 4 had type 2 (2 2A, 1 2B, and 1 2M), and 4 had type 3 VWD. Of the 10 deliveries, 5 were by cesarean section. Patients received a mean of 9.5 infusions of wilate over 6.8 exposure days, with a mean total dose of 234 IU/kg per delivery and 25 IU/kg per infusion. Hemostatic management for all deliveries was rated excellent or good, with no excessive bleeding during delivery and no postpartum bleeding during the period of wilate treatment in any patient. Two patients experienced 8 possible or probable treatment-related adverse events; all were mild or moderate and resolved. No thromboembolic events were observed.

Conclusion: The results of this case series indicate that wilate provided effective hemostatic cover for childbirth in females with VWD during delivery and postpartum.

KEYWORDS
parturition, postpartum hemorrhage, pregnancy, von Willebrand disease, von Willebrand factor

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1 | INTRODUCTION

In healthy females, von Willebrand factor (VWF) and factor (F)VIII levels rise throughout pregnancy [1], with the most dramatic rises observed in the third trimester [1,2]. The levels remain elevated until at least the third day postpartum [3] and return to baseline approximately 3 weeks after delivery [4]. These hemostatic adaptations are believed to have evolved to protect against childbirth-associated hemorrhage [5].

von Willebrand disease (VWD) is caused by a quantitative or qualitative defect in VWF that leaves patients vulnerable to excessive bleeding [6], with some subtypes also associated with reduced FVIII levels [6]. The normal increases in VWF and FVIII seen during pregnancy may be reduced or absent in VWD patients [2], resulting in an increased risk of postpartum hemorrhage (PPH) and other complications during pregnancy [7,8]. In a US-based analysis, females with VWD had a 1.5-fold higher risk of PPH, a 5-fold higher risk of transfusion, longer hospital stays, and a 10-fold higher maternal mortality rate compared with females without VWD [7]. PPH occurs in an estimated 2% to 5% of deliveries in higher socioeconomic countries but is the leading cause of maternal mortality worldwide [9]. Given that a rate of PPH as high as 59% has been reported in females with VWD [9], improving hemostatic management during and after childbirth remains an important unmet clinical need.

Evidence-based recommendations for target VWF levels in VWD patients during pregnancy are lacking, with current practice based on expert opinion. Hemostatic treatment should be initiated if the VWF level is <50 IU/dL [6,10,11]. However, in normal pregnancies, median VWF and FVIII plasma levels can rise to ~200 IU/dL and, in some cases, can reach ~350 IU/dL [1]. Furthermore, the incidence of PPH in females with VWD remains high despite maintaining VWF levels >50 IU/dL [10], suggesting that current practice leaves patients undertreated. Underscoring this, recent guidelines highlighted the need for clinical assessment of the impact of different VWF and FVIII target levels on postdelivery outcomes [12].

wilate (Octapharma AG) is a plasma-derived concentrate containing VWF and FVIII in a 1:1 activity ratio [13,14]. The efficacy and safety of wilate for the prevention and treatment of bleeding in patients with all types of VWD, including during surgery, have been demonstrated in prospective clinical trials [13,15–17]. Here, we describe data for patients with VWD who received wilate during/after childbirth in 2 prospective studies [16,18].

2 | METHODS

Patients who received wilate for childbirth in the 'wilate in subjects with von Willebrand disease who undergo surgery' (WONDERS) [16] or WIL-20 [18] clinical studies were identified. Both studies were conducted in accordance with the Declaration of Helsinki. Patient demographics and data from childbirth until completion of patient follow-up in the study were extracted, including information on perioperative efficacy, bleeds, adverse events (AEs), and plasma levels of VWF and FVIII.

The WONDERS study (NCT01365546) was a prospective, open-label phase 3 trial of the perioperative efficacy and safety of wilate [16]. A loading dose of 40 to 60 IU/kg of VWF ristocetin cofactor (VWF:RCo) within 3 hours of the start of the procedure was given to achieve a peak plasma VWF:RCo level of 100%. A maintenance dose of 20 to 40 IU/kg of VWF:RCo or half of the loading dose was given every 12 to 24 hours to maintain trough levels of VWF:RCo >50% for ≥6 days [16]. Patients were followed for 30 days from surgery start or until discharge, whichever came last. FVIII coagulation activity, VWF:RCo, and VWF antigen levels were measured within 30 minutes before and after wilate infusions. Hemostatic efficacy was assessed by the surgeon and investigator and by an Independent Data Monitoring Committee (IDMC) using a 4-point scale. Based on these assessments, the IDMC rated each surgery as a "success" or "failure" [16].

WIL-20 (NCT01602419) was an observational, prospective, phase 4 study of wilate safety, tolerability, and efficacy in real-world clinical practice [18]. Patients were followed for up to 2 years in the study. For the purposes of this analysis, data up to 12 weeks postpartum were analyzed. In patients who underwent surgery, dosing was at the discretion of the treating physician, with the recommendation to collect FVIII coagulation activity, VWF:RCo, and/or VWF antigen levels throughout the perioperative period. Hemostatic efficacy was assessed using a 4-point scale by the physician for interventional procedures [18].

This Brief Report describes data for patients who received wilate for hemostatic coverage for childbirth in the WONDERS and WIL-20 studies. Dosing data include only infusions indicated by the investigator as given for childbirth. Concomitant treatments for childbirth were any relevant treatment given during the period from first wilate infusion to the end of the postpartum follow-up period.

3 | RESULTS AND DISCUSSION

Ten patients from 6 centers in Canada, Colombia, India, United States, and Uruguay received wilate during/after childbirth, 4 in the WONDERS study between 2012 and 2014 and 6 in the WIL-20 study between 2010 and 2016. The mean age at enrolment was 29.6 years (range, 23-36). Two patients had type 1, 4 had type 2 (2 2A, 1 2B, and 1 2M), and 4 had type 3 VWD. Six patients were Caucasian, 3 were South Asian, and 1 was classified as "Other." Six had blood type O, and 2 each had type A and type B.

Of the 10 deliveries, 5 were by cesarean section and 5 were vaginal deliveries, of which 2 required episiotomy (Table 1). Patients received a mean (SD) of 9.5 (2.2) wilate infusions for childbirth over 6.8 (1.9) exposure days and a total dose of 234 (126) IU/kg per delivery and 25 (15) IU/kg per infusion. All patients received at least one wilate loading dose prior to delivery. More than 1 loading dose was administered in some patients, highlighting the challenge of repeated dosing and prolonged labor (Table 1). Loading doses ranged from 10 to 65 and from 26 to 63 IU/kg per infusion in those who underwent

TABLE 1 Delivery details and wilate dosing for childbirth.

Pt. no.	Study	VWD type	Delivery type	Anesthesia	wilate dosing, total dose (IU/kg) (no. of infusions)			Total EDs	Total days	Postpartum follow-up period
					Loading	Maintenance	All			
1	WIL-20	1	Planned CS	Epidural	11 (1)	62 (10)	73 (11)	7	10	9 d
2	WIL-20	1	Vaginal	Epidural	60 (1)	75 (4)[a]	135 (5)	2	2	2 d
3	WONDERS	2B	Planned CS	General	169 (3)[b]	242 (8)	412 (11)	8	10	29 d
4	WIL-20	2A	Planned CS	NA	10 (1)	45 (8)	55 (9)	9	10	12 wk
5	WIL-20	2A	Vaginal	NA	49 (1)	174 (11)	222 (12)	7	7	12 wk
6	WIL-20	2M	Planned CS	NA	62 (1)	278 (9)	340 (10)	6	7	7 d
7	WONDERS	3	Emergency CS	General	85 (2)[c]	186 (7)	271 (9)	8	9	29 d
8	WIL-20	3	Vaginal	NA	79 (2)[d]	329 (10)	408 (12)	7	8	12 d
9	WONDERS	3	Vaginal (episiotomy)	NA	104 (2)[e]	125 (6)	229 (8)	8	8	27 d
10	WONDERS	3	Vaginal (episiotomy)	NA	49 (1)	148 (7)	197 (8)	7	7	30 d

CS, cesarean section; ED, exposure day; NA, not available, Pt., patient; VWD, von Willebrand disease; WONDERS, wilate in subjects with von Willebrand disease who undergo surgery.

[a] Patient 2 received continuous wilate infusion for maintenance dosing over 30 hours, which was counted as 4 separate infusions.

[b] Patient 3 received an unplanned loading dose (65.1 IU/kg) for early induction of labor via vaginal delivery 1 day prior to the planned cesarean section. Approximately 12 hours later, a second (planned) dose (52.4 IU/kg) was administered; however, as labor stalled, another dose (52.4 IU/kg) was given approximately 8 hours later and the cesarean section was performed.

[c] Patient 7 received loading doses of 42.4 IU/kg 22 hours and 1.3 hours prior to cesarean section.

[d] Patient 8 received loading doses of 52.6 and 26.3 IU/kg on the day of vaginal delivery.

[e] Patient 9 received loading doses of 62.5 IU/kg and 41.7 IU/kg 15.5 hours and 4.3 hours prior to vaginal delivery, respectively.

cesarean sections and vaginal births, respectively (Table 1). The mean duration of maintenance dosing was 7.4 days (8.2 and 5.6 days for cesarean sections and vaginal deliveries, respectively). The mean maintenance dose per exposure day was 30 IU/kg (27 and 31 IU/kg for cesarean sections and vaginal deliveries, respectively). The corresponding doses per infusion were 21, 19, and 22 IU/kg, respectively.

The treatment duration in the present analysis was consistent with that of a multicenter prospective observational cohort study in females with VWD, in which 16/35 pregnancies were managed with postpartum VWF concentrate for a median of 6 days (range, 0-21) [4]. Similarly, in a retrospective registry study, females with VWD who were treated with a VWF concentrate received daily postpartum treatment for a median of 9 days (range, 1-18) [8].

Two patients received concomitant tranexamic acid. Patient 2, a 26-year-old with type 1 VWD, received 2 g of tranexamic acid orally on the day of delivery, followed by 1 g orally 3 times daily for 3 weeks. Patient 10, a 30-year-old with type 3 VWD who underwent a vaginal episiotomy, received concomitant tranexamic acid (1 g every 6 hours) from day 4 after delivery for 11 days. Patient 3, a 29-year-old with type 2B VWD, received 10 planned 250-mL platelet infusions for thrombocytopenia: 6 preoperative, 1 intraoperative, and 3 postoperative. Patient 7, a 25-year-old with type 3 VWD, received a planned preoperative 275-mL red blood cell (RBC) transfusion.

Hemostatic efficacy was rated excellent in all 6 patients in WIL-20. In the WONDERS study, intraoperative and postoperative hemostatic efficacy was rated excellent or good by the surgeon or physician for all 4 patients, and all 4 procedures were classified as successful by the IDMC. No excessive bleeding during delivery was noted for any of the patients, and the amount of blood loss was within the expected range. Patient 9 received a 300-mL RBC infusion 2 days after childbirth due to an unexplained decrease in hemoglobin. Patient 3 received 2 RBC infusions of 300 mL the day after childbirth due to unexplained anemia.

No bleeds occurred in any patient during wilate maintenance treatment after childbirth. After this period, 3 patients experienced 4 bleeds within the remaining postpartum follow-up period. Two bleeds were vaginal bleeds occurring in 2 patients 15 and 18 days after delivery (Figure 1). Patient 4, a 29-year-old with type 2A VWD, experienced a minor secondary PPH 5 days after the last maintenance infusion. This was treated with daily infusions of 10 IU/kg of wilate over 2 days, with overall treatment efficacy deemed excellent by both the patient and investigator. Patient 10 experienced a serious secondary PPH of moderate intensity 11 days after the last maintenance infusion and 4 days after receiving wilate (16.4 IU/kg) for resuturing of an episiotomy. The bleed resolved without sequelae the next day, and tranexamic acid (500 mg every 6 hours) was administered for the next 12 days. The other 2 bleeds that occurred within 12 weeks of delivery were classified as menstrual bleeds by the investigators. One was a minor bleed 43 days after delivery and 33 days after the last maintenance infusion (patient 4); this was treated with 2 doses of 5 IU/kg of wilate, and efficacy was rated as excellent. The other, documented as menorrhagia of moderate intensity by the investigator, occurred 23 days after delivery and 17 days after the last maintenance infusion (patient 9). This was treated with a single

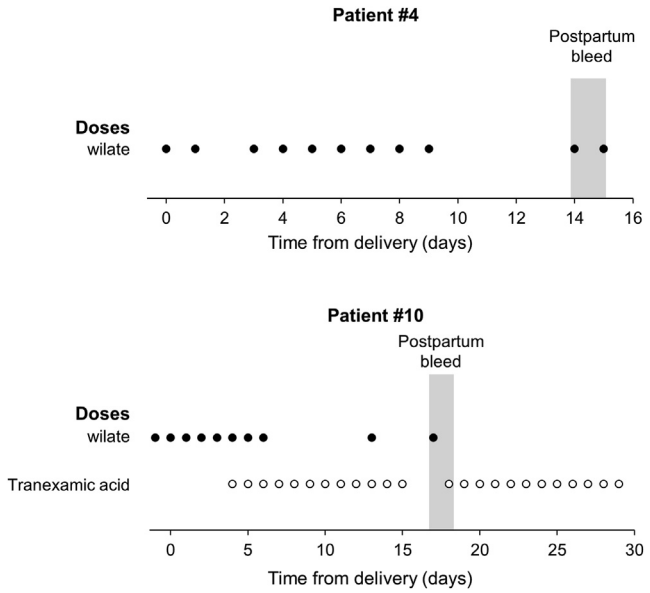

FIGURE 1 Postpartum bleeds after cessation of wilate maintenance infusions for childbirth.

dose of wilate (21 IU/kg) with unknown efficacy. Given that this bleed occurred 23 days after delivery, it is possible that this bleed (as well as the bleed 43 days after delivery) might have been a secondary PPH rather than a menstrual bleed as documented by the investigator.

Although factor levels were unknown at the time of the 2 cases of documented secondary PPH, the fact that both occurred after VWF cessation highlights the importance of postpartum VWF prophylaxis duration. Secondary PPH is defined as occurring between 24 hours and 6 to 12 weeks postpartum [9]; however, guidelines do not recommend a minimum duration or VWF cutoff levels for discontinuation [12]. A global survey on clinical management of pregnancy in VWD patients demonstrated that, depending on the mode of delivery, only 28% to 34% of respondents recommended a postpartum treatment duration of 7 to 14 days [19]. Govorov et al. [8] reported 2 cases of secondary PPH out of 43 pregnancies in VWD patients who received prophylaxis for childbirth according to published recommendations; however, it is unclear whether these PPH cases occurred during prophylaxis or after its discontinuation.

Two patients experienced treatment-related AEs. Patient 3 experienced chest discomfort, feeling hot, and dizziness 8 days after delivery, after the 8 (final) maintenance dose. Patient 8 experienced nausea, shortness of breath, hypotension, tachycardia, and chest discomfort 11 days after delivery, and the infusion was stopped. All AEs were nonserious, mild or moderate in intensity, and resolved. No thromboembolic events were observed.

As expected, coagulation factor levels increased after wilate administration both before and after childbirth in 5 patients with available data (Table 2). Overall, the VWF:RCo plasma levels achieved after childbirth were lower than would be expected in females without VWD [4,20] and below target levels in some cases (Table 2, Figure 2). This suggests that further investigation into the relationship between dose and VWF plasma levels in childbirth is needed and highlights the importance of monitoring VWF:RCo. Parallel changes in VWF and FVIII activity over time were observed, with no FVIII accumulation throughout the postoperative period in any of the patients.

Limitations of this analysis include the differing study designs, the lack of a control arm, and the relatively short follow-up, which did not cover the entire 12-week postpartum period for monitoring of secondary PPH in 8 of the 10 patients. Furthermore, data on peripartum coagulation factor levels were only available for 1 of the 6 patients in WIL-20. The small number of patients described in the present analysis is insufficient to draw firm conclusions regarding recommended

TABLE 2 Coagulation factor levels (international units per deciliter) before and after loading/maintenance doses of wilate (international units per kilogram).

	Loading dose period							Maintenance dose period						
		Coagulation factor levels before and after loading doses							Coagulation factor levels before and after maintenance doses					
		VWF:RCo		VWF:Ag		FVIII:C[b]			VWF:RCo		VWF:Ag		FVIII:C[b]	
Pt. no.	Dose[a]	Before	After	Before	After	Before	After	Dose	Before	After	Before	After	Before	After
2	60	30	112	31	149	120	186	21 (5)	NA	104 (54)	NA	134 (55)[c]	NA	182 (63)[c]
3	65	20	154	51	217	43	181	30 (13)	99 (65)	185 (67)	180 (104)	305 (96)	172 (79)	269 (70)
7	42	<3	53	<3	70	0	65	27 (3)	16 (16)	53 (23)	33 (22)	88 (36)	57 (18)	101 (21)
9	63	5	82	<3	104	0	87	21 (0)	27 (30)	40 (23)	19 (7)	51 (18)	38 (12)	76 (17)
10	49	<3	40	<3	59	1	42	21 (8)	18 (7)	54 (18)	24 (9)	73 (31)	34 (5)	69 (17)

Coagulation factor levels are expressed as single values for loading doses and as mean (SD) for maintenance doses.

FVIII:C, factor VIII coagulation activity; NA, not available; Pt., patient; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor.

[a] Data are for the first loading dose for patients 3, 7, and 9.

[b] Chromogenic assay in patients 3, 7, 9, and 10 within 30 minutes before and after dosing (WONDERS). Assay is unspecified in patient 2 (WIL-20).

[c] Measurements were taken during continuous infusion.

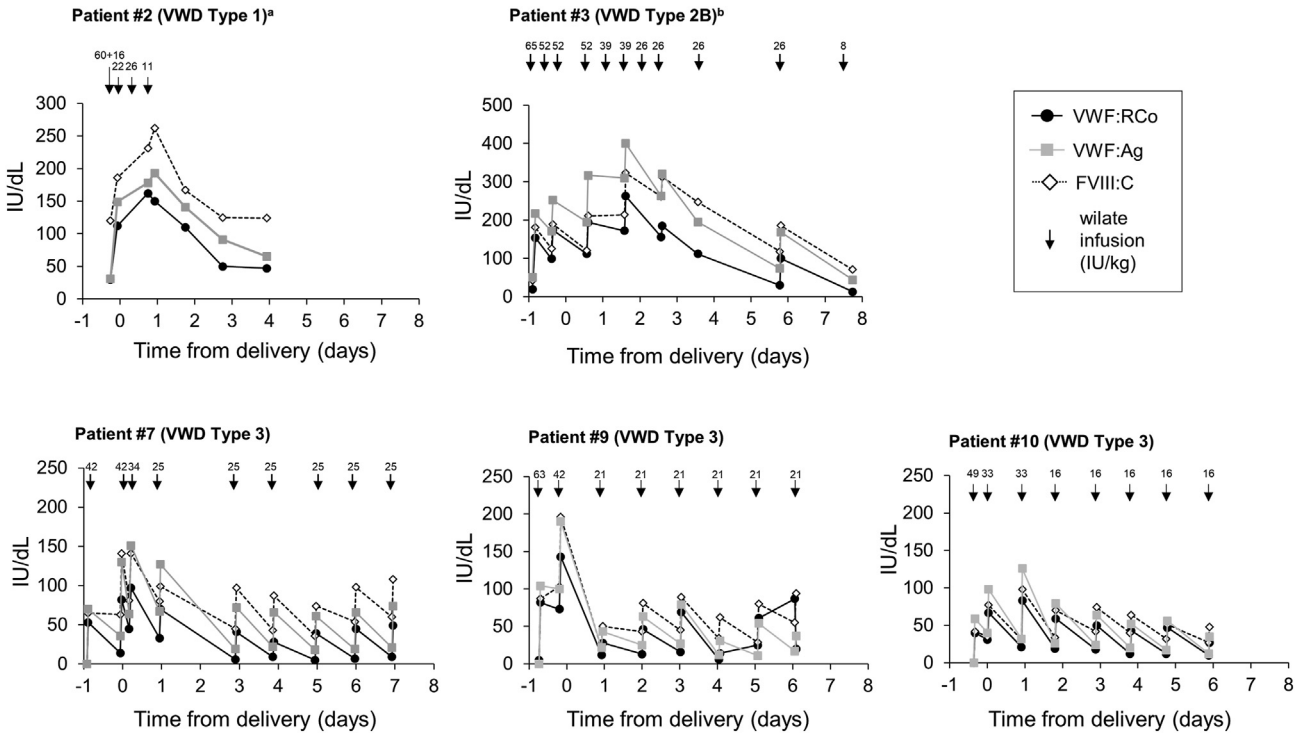

FIGURE 2 Peripartum plasma concentrations of von Willebrand factor (VWF) and factor (F)VIII. [a]For patient 2, postdose coagulation factor levels were measured during and after continuous infusion. [b]For patient 3, postinfusion coagulation factor data were missing after infusions 2, 5, 9, and 11. FVIII:C, factor VIII coagulation activity; VWD, von Willebrand disease; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor.

treatment approaches and outcomes, and future studies are needed to address these points.

In conclusion, the results of this case series indicate that wilate provided effective hemostatic cover in females with VWD during delivery and postpartum.

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AUTHOR CONTRIBUTIONS

A.I. analyzed the data and wrote the first draft of the manuscript. A.I., P.J., A.M., and A.S. assisted with patient recruitment, reviewed the draft manuscript, and agreed to its submission in its final form. The corresponding author, A.I., had full access to all the data in the analysis and had final responsibility for the decision to submit for publication.

DECLARATION OF COMPETING INTERESTS

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