# Pregnancy and delivery in women with von Willebrand's disease and different von Willebrand factor mutations

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## ABSTRACT

### Background
Pregnancy in von Willebrand's disease may carry a significant risk of bleeding. Information on changes in factor VIII and von Willebrand factor and pregnancy outcome in relation to von Willebrand factor gene mutations are very scanty.

### Design and Methods
We examined biological response to desmopressin, changes in factor VIII and von Willebrand factor and pregnancy outcome in a cohort of 23 women with von Willebrand's disease characterized at molecular level and prospectively followed during 2000-2007.

### Results
Thirty-one pregnancies occurred during the study period. Remarkably, similar changes of factor VIII and von Willebrand factor were observed after desmopressin and during pregnancy in nine women with R854Q, R1374H, V1665E, V1822G and C2362F mutations. Women with von Willebrand's disease and R1205H and C1130F mutations (17 pregnancies in 12 women) had only a slight increase of factor VIII and von Willebrand factor during pregnancy while their response to desmopressin was marked but short-lived. For these women, two to three desmopressin administrations within the first 48 hours were sufficient to successfully manage vaginal delivery. Two women with recessive von Willebrand's disease due to compound heterozygosity for different gene mutations had a spontaneous, major increase in factor VIII while von Willebrand factor remained severely reduced. Desmopressin increased factor VIII and was clinically useful in the first case, while a factor VIII/von Willebrand factor concentrate was required in the second patient not responsive to the compound. Factor VIII/von Willebrand factor concentrate was also required for two women with type 2 A von Willebrand's disease with V1665E mutations who had no von Willebrand factor activity change during pregnancy. In one of them, delayed bleeding occurred 15 days later requiring treatment with Factor VIII/von Willebrand factor concentrate. No miscarriages or stillbirths occurred.

### Conclusions
Close follow-up and detailed guidelines for the management of parturition have produced a very low rate of immediate and late bleeding complications in this setting. Desmopressin was effective and safe in preventing significant bleeding at delivery in most of these patients.

Key words: von Willebrand's disease, inherited bleeding disorders, von Willebrand factor- gene mutation, pregnancy, desmopressin.

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## Introduction

Pregnancy and delivery are considered situations predisposing to a high risk of bleeding in women with von Willebrand's disease (VWD).[1,2] While patients with mild deficiency usually show a spontaneous complete correction of basal low factor VIII (FVIII) and von Willebrand factor (VWF) levels during pregnancy, patients with dysfunctional (type 2) or severe (type 3) VWD usually require replacement treatment to avoid immediate or delayed bleeding.[3,4] Despite the fact that several studies have addressed the risk of bleeding at parturition, very few have evaluated FVIII and VWF changes during pregnancy, the bleeding risk and treatment modality in relationship to the specific VWF gene mutations and response to desmopressin. We recently reported a favorable clinical outcome at delivery using desmopressin in a few women with VWD associated with C1130F mutation[5] and R1205H (VWD Vicenza),[6] in whom FVIII and VWF increased poorly during pregnancy. In contrast, FVIII and VWF were fully corrected by the end of pregnancy in a woman with homozygous type 2N VWD with the R854Q mutation and she required no specific treatment.[7]

We report here changes in FVIII and VWF after desmopressin and during pregnancy along with clinical outcome in a series of women with VWD for whom a specific VWF gene mutation and biological response to a desmopressin test infusion were known.

## Design and Methods

Twenty-three women with VWD, previously diagnosed and regularly followed at the Hemophilia and Thrombosis Center of Vicenza, were included in this study. Six patients (of whom two have been previously reported) had a R1205H mutation (VWD Vicenza), six (of whom one has been previously reported) had a C1130F mutation, three had a C2362F mutation, two (one previously reported) were homozygotes for R854Q, one had V1822G, one had R1374H, one was a compound heterozygote for a splice site mutation in intron 13 and novel Q77stop mutation and one had a whole gene deletion and a C2671Y missense mutation. Two women had a typical type 2 A VWD mutation (V1665E).

A bleeding questionnaire was administered to each enrolled family member. The full bleeding questionnaire and criteria used to compare the resulting bleeding score are available at *http://www.shef.ac.uk/euvwd/bleed_score.htm*.

Over a period of 8 years (2000-2007), these patients were prospectively followed during pregnancy, with FVIII/VWF measurements assessed and clinical examinations performed every 3 months or as required. The last examination occurred within 2 to 3 weeks before delivery. Blood loss at delivery was estimated from the loss occurring during parturition, with the blood being collected whenever possible into a plastic bag beneath the patient on the delivery bed.

A test infusion of desmopressin had been previously administered to all the patients while they were not pregnant and the biological response had been evaluated by monitoring FVIII and VWF for at least up to 4 hours after the desmopressin infusion.[8] Informed consent had been obtained from each patient prior to the test infusion with desmopressin. FVIII:C, VWF antigen (VWF:Ag) and VWF ristocetin cofactor activity (VWF:RCo) were assessed as previously described.[8]

## Results

### Phenotypic results

The baseline characteristics of the 23 patients enrolled in the prospective study are summarized in Table 1. A variable severity of deficiencies was observed, the lowest FVIII and VWF levels being present in the women with C1130F and R1205H mutations and in the two compound heterozygotes. The bleeding score was increased in all the patients, apart from those carrying the C2362F mutation.

### Desmopressin test infusion

The FVIII/VWF levels before and 1, 2, and 4 hours after the desmopressin infusion are shown in Figures 1 and 2. The increase of VWF and especially of FVIII 1 hour after the infusion in women with R1205H and C1130F mutations was remarkable and the levels remained relatively high also 2 hours later, with a more rapid return to baseline for those with the R1205H mutation. Patients with V1822G and C2362F mutations had somewhat higher basal FVIII:C and VWF levels, which were completely corrected by desmopressin. Patients with R1374H and V1665E mutations had a robust increase in FVIII:C and normalized VWF:Ag, but VWF:RCo remained significantly lower, particularly in those with the V1665E mutation. While the patient with compound heterozygosity for the splice site mutation in intron 13 and Q77stop mutation had a significant, isolated increase in FVIII:C increase, no increase of any of the moieties was evident for the woman with a whole gene deletion and the C2671Y missense mutation. The two patients with homozygous R854Q mutations had full FVIII:C normalization.

### Influence of pregnancy on factor VIII and von Willebrand factor measurements

FVIII and VWF measurements during pregnancy until delivery are illustrated in Figures 1 and 2. FVIII:C remained always below 25 IU/dL and VWF below 20 IU/dL, even at the end of pregnancy, in women with the R1205H mutation, while a slightly greater increase in FVIII:C was evident in women with the C1130F mutation. A full correction of all the moieties was observed in the women with V1822G, C2362F or R854Q mutations. The two patients with compound heterozygosity showed an isolated increase of FVIII:C, while the women with V1665E and R1374H mutations had normalization of FVIII:C and VWF:Ag but persistent, abnormally low levels of VWF:RCo (Figure 2).

### Pregnancy and delivery outcome

The details of the outcome of previous and present pregnancies are summarized in Table 1. Only the woman with a R1374H mutation had a threatened spontaneous miscarriage with intermittent vaginal bleeding in the first 3 months of both her pregnancies and was treated with progesterone. A total of 31 deliveries were studied. None of the patients required a Cesarean section. All the women with R1205H and C1130F mutations (17 deliveries) were given desmopressin immediately after vaginal delivery and section of the umbilical cord. A midline episiotomy was carried out in five cases, without complications, and wound healing was normal. A second infusion of desmopressin was administered 24 hours later and a third dose 48 h after the first in the five women undergoing episioto-

my. No excessive bleeding was observed for these 17 deliveries and the measured blood losses were approximately less than 300 mL in five cases and less than 500 mL in six; no measurements were made in the other six deliveries. The patients were discharged from hospital on day 5 post-partum. No excessive bleeding was observed in the late puerperium and no further treatment was required. No treatment was administered to the three women with a C2362F mutation or R854Q mutation and no undue bleeding occurred. On the day 2 post-partum FVIII:C was still around 60 IU/dL in the R854Q homozygous women. The woman with V1822G was treated with a single desmopressin infusion to provide more robust increases in FVIII and VWF and she had no bleeding complications from her two deliveries. The patient with an R1374H mutation was empirically treated with two doses of desmopressin 12 hours apart since her increase in VWF:RCo was insufficient (32 IU/dL at the end of pregnancy) compared to FVIII and VWF:Ag. She had no bleeding with her two deliveries. The woman who was a compound heterozygote for the Q77stop mutation and the splice site mutation in intron 13 refused treatment with FVIII and VWF concentrates. Desmopressin was administered and a second dose 24 hours later advised since the patient delivered at another hospital. Unfortunately, the second dose was not administered and the patient had vaginal bleeding on day 5 post-partum, which was successfully treated with a FVIII and VWF concentrate. Her second delivery was treated with the two recommended doses and the patient did not have any immediate or delayed bleeding. The woman with compound heterozygosity for gene deletion and C2671Y was treated with FVIII/VWF concentrate without mishap. Excessive bleeding with lochia was reported; it was easily controlled with oral tranexamic acid. The two women with a V1665E mutation had three pregnancies: the first had two deliveries covered with a FVIII/VWF concentrate, but suboptimal treatment during the first delivery was followed by delayed bleeding requiring two additional doses at 24-hour intervals. The second was treated in a similar way (40 IU/kg FVIII during labor, then 25 IU/kg 48 and 72 hours later) but bleeding occurred 15 days later, requiring two infusions of the concentrate 24 hours apart. At that time, her VWF:RCo was 7 IU/dL and FVIII:C 51 IU/dL.

None of the woman had signs of water intoxication or serum electrolyte abnormalities prior to discharge.

Nineteen neonates had a mutant VWF allele (ten either R1205H or C1130F, two R854Q, two Q77stop, one C2362F, one C2671Y, one V1822G, one V1665E and one R1374H), but no bleeding complications occurred during parturition or the neonatal period in these babies.

## Discussion

Women with VWD are at particular risk of bleeding complications during their lifetime and usually their bleeding severity, as assessed by a standardized bleeding

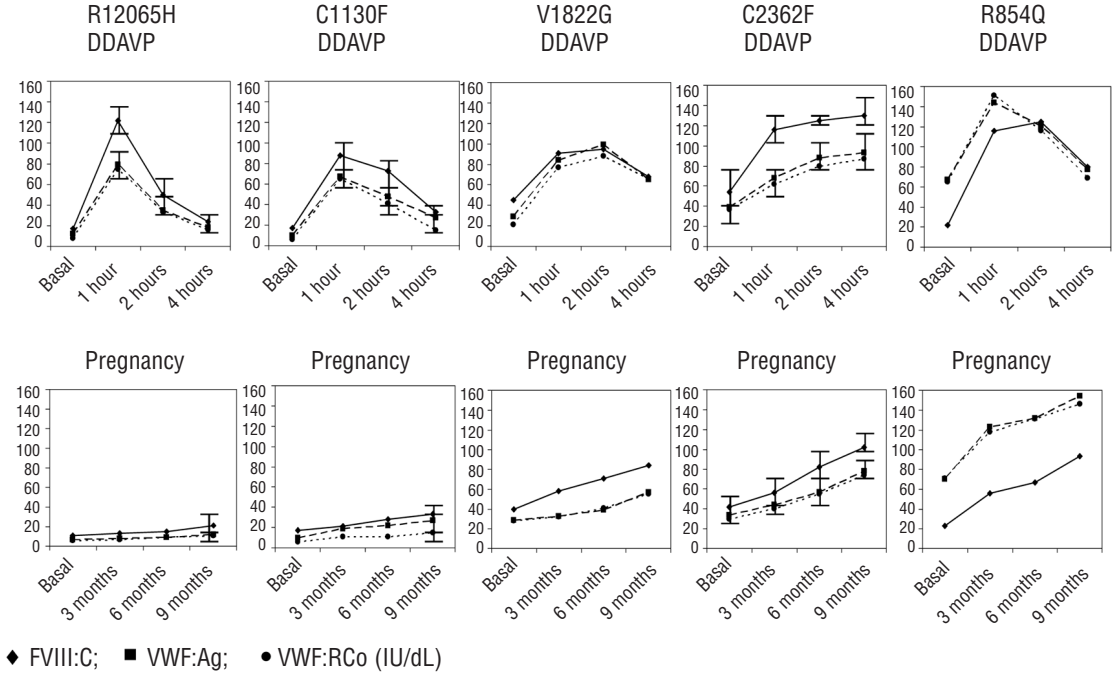


**Figure 1.** Upper part. FVIII:C and VWF measurements before and after desmopressin infusion (0.3 μg/kg body weight). For women with R1205H and C1130F mutations, the results are the average ± SD of a single test in six patients each, for V1822G the results are of a single test, for C2362F the results are the average±SD of a single test in three patients, for R854H the results are the average for two patients. Lower part. FVIII:C and VWF changes during 12, 24 and 36 weeks of pregnancy. For R1205H and C1130F, the results are the average±SD of a single pregnancy in six patients each, for V18229 the average of two pregnancies for C2362F, the average ±SD of a single pregnancy in three patients and for R854Q, the average of two pregnancies.

score, is more relevant than that of males with VWD.[9] The large majority of our patients had a significant bleeding score (> 3) and thus the risk of bleeding at parturition might have been significant.[9] Only those carrying the C2362F mutation had a normal bleeding score, in keeping with previously reported findings.[10] Women with VWD are at increased risk of post-partum hemorrhage if untreated (with an incidence of up to 29% compared to an incidence of 3-5% in the general population)[12] and the risk may persist if anti-hemorrhagic prophylaxis at delivery is not adequate.[11] A recent case-control study of 4,067 deliveries in VWD showed that women with VWD have a higher risk of primary post-partum hemorrhage (odds ratio 1.5) and five-fold greater risk of being transfused.[13] However, despite this general appreciation of the bleeding risk associated with delivery in VWD, very few data are available on the relationship of FVIII and VWF changes during pregnancy, bleeding risk and treatment modality according to the various causative VWF gene mutations.

In this prospective study, 31 consecutive pregnancies occurring during 2000-2007 in 23 VWD females with known VWF gene defects and information available from a desmopressin test-infusion carried out while the women were not pregnant were analyzed. Given the case selection, the large majority of these women had a severe phenotype, with FVIII:C and/or VWF basal levels less than 20 IU/dL (Table I), at variance with women previously reported in other studies.[4] In mild cases of VWD, normalization of FVIII and VWF activities at the end of pregnancy is usually observed and prophylactic treatment is seldom required.[1,2] Remarkably, similar FVIII and VWF changes were observed after desmopressin and during pregnancy in women with R854Q, R1374H, V1665E, V1822G and C2362F mutations (Figures 1 and 2), even though the factor increase was, on average, 20% greater after desmopressin; thus, the results of a test infusion could be assumed to predict FVIII and VWF changes during pregnancy in these patients. A discrepant pattern was observed in patients with C1130F and R1205H mutations. These patients have a shortened VWF survival after desmopressin, but they are able to attain very high levels shortly after infusion.[14,15] Thus, despite the fact that no significant changes of FVIII/VWF levels were observed during pregnancy, delivery was successfully covered with desmopressin infusions. A schedule of 24-hour intervals was chosen to minimize the risk of tachyphylaxis and the compound was administered soon after delivery to avoid possible risks to the newborn. A single report demonstrated the safety of desmopressin in pregnant women, but only during the first trimester of pregnancy.[16] The importance of desmopressin prophylaxis is highlighted by the fact that 13/15 pregnancies in other women with VWD Vicenza, carried out in the past prior to the diagnosis without specific antihemorrhagic prophylaxis, were followed by significant bleeding at parturition and blood transfusion was required in 11/13 (*Castaman G & Rodeghiero F, unpublished observations*). Interestingly, even though FVIII/VWF remained low, no delayed bleeding was

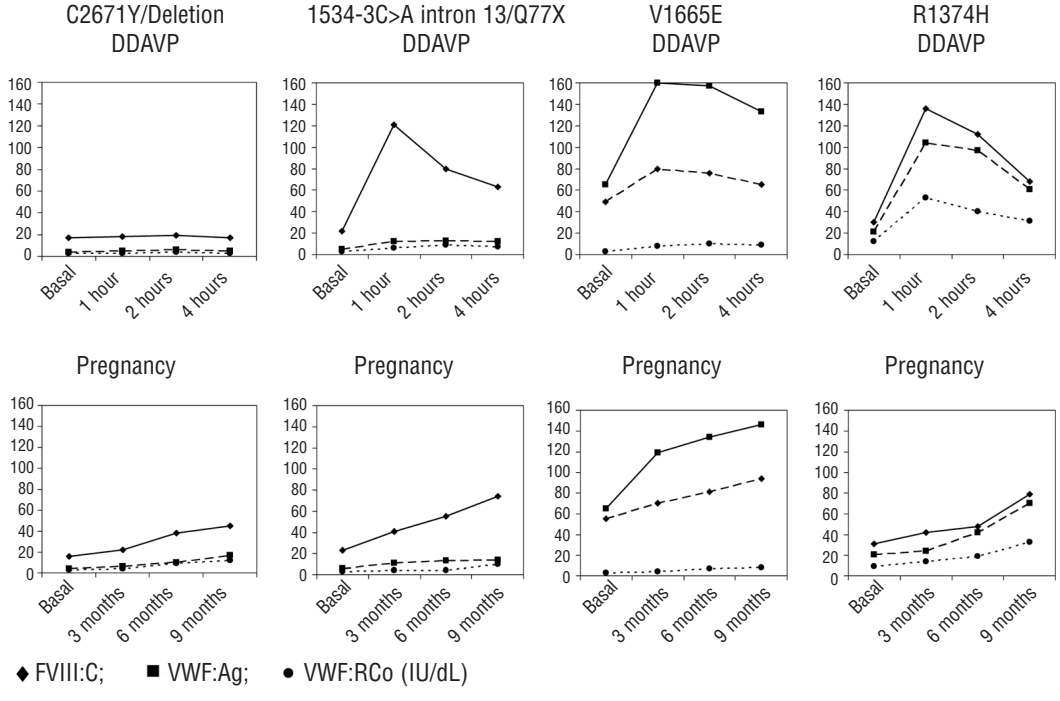


**Figure 2.** Upper part. FVIII:C and VWF measurements before and after desmopressin infusion (0.3 μg/kg body weight). For C2671Y/deletion, 1534-3C>A intron 13/Q77X and R1374H, the result of a test-infusion is reported, for V1665E the average of the results of a test-infusion in two patients is reported. Lower part. FVIII:C and VWF changes at 12, 24 and 36 weeks of pregnancy. The results represent the mean of two different pregnancies, apart from the patient with C2671Y/gene deletion.

**Table 1.** Main laboratory characteristics and obstetric history in the investigated women.

| Case and type of VWD | Bleeding Score | VWF mutation | Age at delivery (years) | Basal FVIII (IU/dL) | Basal VWF:Ag (IU/dL) | Basal VWF:RCo (IU/dL) | Previous deliveries | Present outcome |
|---|---|---|---|---|---|---|---|---|
| 1-2 N | 6 | R854Q homozygous | 34 | 22 | 63 | 65 | One, without anti-hemorrhagic prophylaxis. No bleeding | One, without anti-hemorrhagic prophylaxis, no bleeding |
| 2-2 N | 5 | R854Q homozygous | 32 | 26 | 68 | 61 | One, without anti-hemorrhagic prophylaxis. Oozing during puerperium. No treatment | One, without anti-hemorrhagic prophylaxis, no bleeding |
| 3-2 A | 7 | C1130F | 20 - 22 | 18 | 9 | 6 | None | Two, two desmopressin doses, no bleeding |
| 4-2 A | 8 | C1130F | 21 | 17 | 11 | 7 | None | One, three desmopressin doses, no bleeding |
| 5-2 A | 8 | C1130F | 25 - 27 | 18 | 10 | 6 | None | Two, one with two and one with three desmopressin doses, no bleeding |
| 6-2 A | 10 | C1130F | 29 | 17 | 9 | 7 | One, successfully treated with desmopressin | One, two desmopressin doses, no bleeding |
| 7-2 A | 10 | C1130F | 30 | 14 | 10 | 6 | One, successfully treated with desmopressin | One, two desmopressin doses, no bleeding |
| 8-2 A | 12 | C1130F | 38 | 19 | 12 | 7 | Two, successfully treated with desmopressin | One, three desmopressin doses, no bleeding |
| 9-1 | 10 | R1205H | 22 | 8 | 5 | 5 | None | One, two desmopressin doses, no bleeding |
| 10-1 | 9 | R1205H | 25 - 28 | 9 | 5 | <3 | None | Two, one with two and one with three desmopressin doses; no bleeding |
| 11-1 | 6 | R1205H | 26 - 30 | 11 | 6 | <3 | None | Two, two desmopressin doses, no bleeding |
| 12-1 | 5 | R1205H | 29 | 9 | 7 | 6 | None | One, three desmopressin doses, no bleeding |
| 13-1 | 11 | R1205H | 30 - 33 | 10 | 5 | 5 | None | Two, two desmopressin doses, no bleeding |
| 14-1 | 10 | R1205H | 31 | 9 | 8 | 6 | One, successfully treated with desmopressin | One, two desmopressin doses, no bleeding |
| 15-2 A | 4 | R1374H | 37 -39 | 27 | 21 | 6 | None | Two. Threatened miscarriages, intermittent early bleeding in both. Single desmopressin dose at delivery., no bleeding |
| 16-2 A | 13 | V1665E | 30 | 64 | 41 | 3 | One, vaginal bleeding and perineal hematoma on day 3 due to suboptimal treatment with FVIII/VWF concentrate at another hospital | One, FVIII/VWF concentrate, no bleeding |
| 17-2 A | 12 | V1665E | 36 | 58 | 44 | 3 | None | One, FVIII/VWF concentrate, bleeding on 15th day, further treatment with FVIII/VWF concentrate |
| 18-1 | 8 | V1822G | 26 - 29 | 41 | 26 | 22 | None | Two, single desmopressin dose, no bleeding |
| 19-1 | 2 | C2362F | 27 | 63 | 37 | 33 | None | One, without anti-hemorrhagic prophylaxis, no bleeding |
| 20-1 | 1 | C2362F | 32 | 55 | 32 | 30 | One, without anti-hemorrhagic. prophylaxis, no bleeding | One, without anti-hemorrhagic prophylaxis, no bleeding |
| 21-1 | 2 | C2362F | 33 | 48 | 40 | 39 | One, without anti-hemorrhagic prophylaxis. No bleeding | One, without anti-hemorrhagic prophylaxis, no bleeding |
| 22-1 recessive | 9 | Q77stop/ Intron13 | 33 - 36 | 20 | 7 | 4 | None | Two. First with a single desmopressin dose, bleeding on 5th day; FVIII/VWF concentrate. Second, two desmopressin doses, no bleeding |
| 23-1 recessive | 9 | C2671Y/del | 31 | 11 | 4 | 3 | None | One, FVIII/VWF concentrate, no bleeding Excessive bleeding with lochia controlled with oral tranexamic acid |

*The laboratory results are the mean of at least three separate measurements.*

observed, as reported in other cases of type 1 VWD with similar behavior during pregnancy.[3] Thus, it appears that immediate, efficacious hemostasis could be important in preventing secondary delayed bleeding in these women. C1130F has been included among type 2 A mutations since it is characterized by a relative loss of high molecular weight multimers.[17] However, patients with this mutation have a normal content of platelet VWF,[18] which is considered a good predictor of a useful response to desmopressin.[19] Thus, from the clinical point of view, patients with VWD could be most simply classified according to their response to desmopressin, regardless of their multimeric pattern.

Women with the V1665E mutation who lacked high and intermediate VWF multimers required treatment with a FVIII/VWF concentrate (*data not shown*), while the woman with a R1374H mutation, who has a relative decrease of the largest forms only, benefited from a good increase in VWF:RCo after a desmopressin infusion (Figure 2).[17] Delayed bleeding was observed in one woman with a V1665E mutation and in the other a previous pregnancy was complicated by bleeding because of suboptimal FVIII/VWF concentrate prophylaxis. Thus, in these women full and prolonged correction of the hemostatic abnormality seems to be required to avoid delayed bleeding.

It is generally considered that the correction of FVIII:C in VWD is important for the treatment of soft-tissue and surgical bleeding[20] and that basal levels of FVIII and VWF below 15 U/dL are accompanied by failure to achieve levels greater than 50 U/dL at the end of pregnancy.[21] In our study, two women with compound heterozygosity and a severe phenotype had a peculiar pattern. These women had an isolated, significant increase of FVIII:C alone during pregnancy, which was almost similar to that observed after the test infusion of desmopressin (Figure 2) in the woman with Q77/IVS13 mutations. An uneventful delivery was obtained by using desmopressin alone, while the first delivery was followed by bleeding because of suboptimal treatment. The second patient was completely unresponsive to desmopressin and thus FVIII and VWF concentrate, administered for 2 days (40 IU/Kg FVIII initially and then 25 IU/Kg FVIII 48 and 72 hours later), was required for a successful delivery. The pattern observed in these women emphasizes the importance of monitoring FVIII:C and VWF, at least at the end of pregnancy, since clinical significant increases, at least of FVIII:C, may also occur in patients with a severe recessive phenotype, although different from typical type 3 VWD.

Interestingly, in our cohort of women, threatened spontaneous miscarriage was observed only in two pregnancies in the woman with a R1374H mutation who had intermittent vaginal bleeding in the first trimester. The low rate of miscarriage and vaginal bleeding during pregnancy observed in our patients is at variance with previous observations in a series of patients retrospectively evaluated during 1980-1996.[4]

The identification of mutations among VWD patients is important but cannot be considered the sole parameter useful for determining the clinical severity of VWD, a disorder with wide heterogeneity of phenotypes. Indeed, in this respect, the bleeding score seems to represent a better instrument for appreciating the real risk of bleeding in specific circumstances.[9,22]

Neonates affected by type 3 VWD may be at risk of bleeding complications and, therefore, may require replacement treatment,[23] even though national registries do not report a significant occurrence of bleeding at birth in these patients.[24] However, this risk is even smaller in neonates with other types of VWD,[23] as confirmed in our neonates who did not have any bleeding complications.

In conclusion, for the first time a large number of women with a known VWF mutation have been characterized for their response to desmopressin and changes in FVIII and VWF during pregnancy. Close follow-up and detailed guidelines for the management of parturition have produced a very low rate of immediate and late bleeding complications in such women. Furthermore, it appears that neonatal risk is very small. The persistence of severely reduced FVIII and VWF levels in women with recessive VWD or C1130F or Vicenza is not accompanied by an increased risk of bleeding during pregnancy or at parturition. Finally, desmopressin is effective and safe in preventing significant bleeding at delivery in most women with VWD, even when not all the properties of VWF are fully normalized after desmopressin infusion.

## Authorship and Disclosures

GC designed the research, analyzed data, followed the patients and wrote the manuscript; AT followed the patients, analyzed data and revised the manuscript; FR analyzed data and revised the manuscript.

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