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# Pregnancy in Women with Different Types of Von Willebrand Disease

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**The course and outcome of pregnancy in women with different types of von Willebrand disease (3 type I, 1 subtype IIA, and 1 subtype IIB) are described. In all patients, factor VIII increased and reached normal levels before delivery, whereas the bleeding time remained prolonged; in subtypes IIA and IIB the abnormal multimeric structure of von Willebrand factor remained unchanged. Deliveries were uneventful in all patients, with two spontaneous vaginal deliveries and three cesarean sections, despite the fact that no replacement therapy was given. Hence, the most important determinant of abnormal hemorrhage during delivery is low factor VIII; the prolonged bleeding time can be compensated for by meticulous surgical hemostasis and efficient contraction of the uterus. Replacement therapy with plasma derivatives can usually be avoided providing that normal factor VIII levels have been attained at delivery.** ***(Obstet Gynecol 68:282, 1986)***

Von Willebrand disease is an inherited bleeding disorder of both males and females characterized by an abnormal primary hemostasis, reflected in a prolonged bleeding time, and by a deficiency of plasma factor VIII and von Willebrand factor. Several previous studies[1–15] based on case reports or small series of patients have addressed the problem of hemorrhagic risk during pregnancy and delivery for women with the disease. Analyzing all published reports (22 women, 33 pregnancies), bleeding occurred in 27% of pregnancies at the time of abortion, delivery, or puerperium. This high incidence of bleeding has led to recommendation of very aggressive treatment, based on replacement therapy with plasma cryoprecipitate given at delivery and puerperium.[16] The problem of bleeding complications in pregnancy should now be reviewed in the light of the recent progress in the understanding of von Willebrand disease and of its complex phenotype.[17] The molecular basis of the disease can be either a deficiency or a dysfunction of factor VIII-von Willebrand factor, a complex of two plasma proteins with distinct genetic and biochemical properties assembled in multimers with molecular weight from 1.5 to 20 × $10^6$.[17] The complex can be measured as factor VIII coagulant activity, von Willebrand factor antigen (formerly called factor VIII-related antigen), or ristocetin cofactor, the latter being the property of von Willebrand factor that leads to platelet agglutination in the presence of the antibiotic ristocetin.[17] The most common form of the disease, called type I and characterized by a prolonged bleeding time and equally low plasma levels of factor VIII, von Willebrand factor antigen, and ristocetin cofactor, is usually due to reduced production of normally functioning von Willebrand resulting in a secondary defect of factor VIII.[17] Dysfunctional von Willebrand factor is the pathophysiologic basis of other forms of the disease called type II,

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and in turn subdivided into several subtypes. The subtype called IIA is characterized by the absence of the large and intermediate size multimers and by the absence of ristocetin-induced platelet agglutination in platelet-rich plasma; in the subtype called IIB, only large multimers are absent and ristocetin agglutination is heightened. Other rarer subtypes with more complex multimer abnormalities (IIC and IID) have been recently described.[17]

The problem of bleeding and its management in pregnant women with von Willebrand disease was reexamined on the basis of their differentiation in types and subtypes by following three women with type I, one with subtype IIA, and one with subtype IIB during pregnancy, at delivery, and during the puerperium.

## *Patients and Methods*

Factor VIII was assayed by a one-stage clotting technique,[18] von Willebrand factor antigen by electroimmunoassay,[18] and ristocetin cofactor by aggregometry of formalin-fixed platelets.[18] These measurements were expressed in units per deciliter in plasma, with reference to the International Reference Preparation (National Institute for Biological Standard and Controls, London, England). Bleeding times were obtained in duplicate, using the automatic device Simplate II (General Diagnostic, Milano, Italy). The multimeric structure of von Willebrand factor in plasma was analyzed by sodium dodecylsulphate 1.4% agarose gel electrophoresis, as described.[18] These tests and platelet counts were carried out in the second month of pregnancy, and the results were taken as baseline values because they were very close to those obtained out of pregnancy. Results of the same tests performed in the ninth month of pregnancy were taken as prepartum values.

Five women (age range: 20 to 33 years), with diagnoses of von Willebrand disease (3 type I, 1 subtype IIA, and 1 subtype IIB) were followed serially during recent pregnancies. Each of them had a lifelong history of postoperatve bleeding, two had had menorrhagia, and one had had wound hematoma and infection after

**Table 1.** Description of Patients and Changes During Pregnancy

| Patient no. | Type or subtype | Factor VIII-von Willebrand factor | Baseline values | Prepartum values | Normal values |
|---|---|---|---|---|---|
| 1, 33 yr, para 0 | I | Factor VIII, U/dL | 35 | 179 | 53–155 |
| | | von Willebrand factor antigen, U/dL | 53 | 168 | 50–160 |
| | | Ristocetin cofactor, U/dL | 33 | 180 | 49–153 |
| | | Bleeding time (min) | 9 | 9 | 3–7 |
| | | Platelet count, $\times 10^9$/L | 145 | 105 | 150–450 |
| | | Multimeric structure | All multimers present | | |
| 2, 20 yr, para 0 | I | Factor VIII, U/dL | 30 | 64 | |
| | | von Willebrand factor antigen, U/dL | 35 | 65 | |
| | | Ristocetin cofactor, U/dL | 40 | 66 | |
| | | Bleeding time (min) | 10 | 10 | |
| | | Platelet count, $\times 10^9$/L | 280 | 269 | |
| | | Multimeric structure | All multimers present | | |
| 3, 24 yr, para 0 | I | Factor VIII, U/dL | 39 | 72 | |
| | | von Willebrand factor antigen, U/dL | 23 | 61 | |
| | | Ristocetin cofactor, U/dL | 6 | 9 | |
| | | Bleeding time (min) | >30 | >30 | |
| | | Platelet count, $\times 10^9$/L | 293 | 155 | |
| | | Multimeric structure | All multimers present | | |
| 4, 22 yr, para 0 | IIA | Factor VIII, U/dL | 38 | 72 | |
| | | von Willebrand factor antigen, U/dL | 96 | 94 | |
| | | Ristocetin cofactor, U/dL | 5 | 11 | |
| | | Bleeding time (min) | >30 | >30 | |
| | | Platelet count, $\times 10^9$/L | 264 | 377 | |
| | | Multimeric structure | Large and intermediate multimers absent | | |
| 5, 26 yr, para I | IIB | Factor VIII, U/dL | 9 | 62 | |
| | | von Willebrand factor antigen, U/dL | 34 | 111 | |
| | | Ristocetin cofactor, U/dL | 11 | 44 | |
| | | Bleeding time (min) | >30 | >30 | |
| | | Platelet count, $\times 10^9$/L | 193 | 138 | |
| | | Multimeric structure | Large multimers absent | | |

a previous cesarean section. Diagnosis of types and subtypes was made by published criteria.[18]

## Results

Table 1 shows the values for relevant hemostatic measurements at the beginning and end of pregnancy in three patients with type I von Willebrand disease (1–3), in one patient with subtype IIA (4), and one with subtype IIB (5). In all the patients, factor VIII and von Willebrand factor antigen increased and reached normal values. Ristocetin cofactor reached normal or borderline values in type I patients 1 and 2 and in the type IIB patient 5, but remained very low in the type I patient 3 and in the type IIA patient 4. The bleeding time, which was minimally prolonged in type I patients 1 and 2 and markedly prolonged at the beginning of pregnancy in the remaining cases, remained prolonged before delivery. Platelet counts decreased slightly in the IIB patient 5 (from 193,000 to 138,000/$\mu$L) and in the type I patient 1 (from 145,000 to 105,000/$\mu$L) and remained unchanged in the remaining three patients. At the beginning of pregnancy, the multimeric structure of von Willebrand factor was intact in patients with type I and remained so at the end of pregnancy (Table 1). At the beginning of pregnancy the IIA patient had no large and intermediate multimers and the IIB had no large multimers. These abnormal patterns did not change by the end of pregnancy (Table 1).

All the pregnancies were term from 37 to 39 weeks' gestation, with spontaneous vaginal deliveries for two cases (2 and 4) and cesarean sections for the remaining three (1, 3, 5). All cesarean sections were carried out because of obstetric complications. Estimated blood losses during or immediately after surgery were normal, despite the fact that no hemostatic treatment was given. Wound healing was uneventful and patients were discharged on the 12th postpartum day. In the two vaginal deliveries, the onset of labor was normal and uterine contractions efficient. Measured blood losses were on the low side of the normal range (200 and 250 mL; normal less than 500 mL), again without hemostatic treatment. Midline episiotomy was uncomplicated in all patients and wound healing was normal, with the patients discharged from hospital on the postpartum day 7. After uneventful pregnancies, labor, and delivery, bleeding complications occurred in the late puerperium in two patients. Patient 3 (type I) had heavy vaginal bleeding and had to be readmitted to the hospital on day 35 after delivery. On admission, her hemoglobin was 5.6 g/dL, and 4 U of packed red cells had to be infused. Bleeding stopped after intravenous administration of desmopressin (0.4 $\mu$g/kg), a synthetic derivative of the antidiuretic hormone that raises factor VIII and von Willebrand factor in plasma.[19] In addition, methylergonovine maleate (0.2 mg) was given every six hours. Hemostatic measurements were not obtained because of the emergency situation. The other bleeding complication occurred in the IIA patient 4, who had mild vaginal bleeding on day 25, promptly controlled by uterine suction and methyl-ergonovine, without anemia and need for blood, blood products, or desmopressin.

## Discussion

In agreement with others,[1,6,7,11,16] the current authors have found that factor VIII and von Willebrand factor antigen increased during pregnancy and reached normal values in five women with von Willebrand disease, irrespective of the type or subtype. Ristocetin cofactor activity remained very low in two patients (3 and 4) and the bleeding time prolonged in all. The finding of Takahashi,[15] that the abnormal multimeric structure of von Willebrand factor in subtype IIA remains unchanged during pregnancy, was confirmed. Also, shown for the first time, the abnormal IIB pattern also remains unchanged. Despite these persisting abnormalities, and the fact that no replacement therapy was given, no bleeding complications occurred during pregnancy, delivery, or early puerperium. In contrast, others found it necessary to infuse cryoprecipitate to stop bleeding during vaginal delivery or cesarean section.[9,11,14] Lipton et al[14] suggested that ristocetin cofactor and bleeding time are the best predictors for risk of bleeding in pregnant women with von Willebrand disease and recommended giving cryoprecipitate at the time of delivery, particularly at cesarean section, if ristocetin cofactor levels were not at least 50% of normal and the bleeding time remained prolonged. Their recommendation contrasts with the fact that two of the current authors' patients (3 and 4) did not bleed abnormally during delivery and early puerperium, even though their ristocetin cofactor levels were very low and the bleeding time very prolonged. Additional evidence that plasma ristocetin cofactor levels are not good reflectors of the abnormal primary hemostasis in von Willebrand disease, comes from the fact that the IIB patient (5) had nearly normal prepartum levels and yet a very prolonged bleeding time. According to the authors' experience[20] and those of others,[21,22] the most important determinant of abnormal surgical bleeding in von Willebrand disease is low factor VIII, which leads to wound hematoma, and the lack of which cannot be compensated for by surgical maneuvers. It is less important to correct the bleeding time, the indicator of an abnormal primary hemostasis, because this can be compensated for by meticulous surgical hemostasis and efficient contrac-



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tion of the uterus after delivery.[20–22] Hence, it is not surprising that the patients who all had normal or borderline factor VIII levels at delivery did not bleed abnormally despite long bleeding time in all and very low ristocetin cofactor in some. Two of the studied patients had bleeding complications in the late puerperium, when they had already been discharged from the hospital. Factor VIII levels could not be assayed at the time of bleeding, so it is not known whether or not they already returned to the low levels measured before pregnancy. However it is likely that this had occurred, because factor VIII is known to return rapidly to baseline levels after delivery.[23] Bleeding, which was severe enough in only one patient to require specific hemostatic treatment, was controlled by the infusion of desmopressin, a derivative of the natural antidiuretic hormone that is known to increase factor VIII and von Willebrand factor, probably through release from stores.[18] However, only patients with type I von Willebrand disease respond favorably to desmopressin, whereas patients with dysfunctional von Willebrand factor (type II) are not responsive.[18] The great potential advantage of desmopressin is that, unlike cryoprecipitate, with this compound there is no risk of transmitting hepatitis. Hence, it might be considered as an alternative to cryoprecipitate when normal factor VIII levels are not attained by the time of delivery.

In conclusion, cryoprecipitate can usually be avoided without risk of bleeding in pregnant women with von Willebrand disease, providing that normal factor VIII levels have been attained at the time of delivery. Careful surgical hemostasis and effective uterine contraction are other requirements for uncomplicated delivery. When factor VIII has not reached hemostatic levels by the time of delivery, desmopressin should be considered instead of cryoprecipitate because it does not carry hepatitis and other infectious disease. However, larger clinical experience is needed before establishing the indications and possible limits of this new hemostatic treatment.

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