

VON WILLEBRAND'S DISEASE IN CONNECTION
WITH THE DELIVERY OF
FEMALE INFANT WITHOUT EXCESS
BLEEDING: A CASE REPORT

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ABSTRACT

A 24-year-old woman with von Willebrand's disease who delivered a female infant vaginally without bleeding problems is described. Blood loss during delivery was 440 ml and within the normal range. Coagulation studies just before delivery revealed a striking improvement of factor VIII (VIII: C: 92% and VIIIIR: AG: 200%), in contrast to those (VIII: C: 38% and VIIIIR: AG: 22%) before pregnancy. However, abnormalities in coagulation studies of bleeding time (8 min), platelet retention rate (33.4%) and VIIIIR: WF (30%) just before delivery remained unchanged, compared with those before pregnancy. The patient delivered a female infant with von Willebrand's disease vaginally without excess bleeding with the infusion of 500ml of fresh frozen plasma. The prophylactic use of factor VIII preparations during delivery of patients with von Willebrand's disease is discussed.

Key words: von Willebrand's disease, Pregnancy, Delivery.

INTRODUCTION

Von Willebrand's disease (vWD) is a hereditary hemorrhagic disorder characterized by normal platelet count, prolonged bleeding time, low level of factor VIII, decreased platelet retention in a glass bead column, abnormal aggregation with ristocetin and "overresponse" of factor VIII activity to infusion of normal plasma or cryoprecipitate.¹⁾ Both sexes are affected because of an autosomal dominant trait.^{1),2)} Spontaneous

manifestations of bleeding are usually mild, but severe hemorrhage is not uncommon during pregnancy and after delivery.²⁾

Recently we encountered a pregnant patient with vWD who delivered a female infant without a bleeding problem. The prophylactic use of factor VIII preparations during delivery in patients with vWD is discussed.

MATERIALS AND METHODS

Platelets were counted by phase contrast microscopy. Bleeding time was determined by the method of Duke.³⁾ Platelet retention in a glass bead column was measured by the Hellem II method.⁴⁾ Factor VIII coagulant activity (VIII: C) was assayed by a one-stage method⁵⁾ using AHF deficient plasma (DADE). Factor VIII-related antigen (VIII:AG) was measured by the method of Zimmerman *et al.*⁶⁾ using Laurell's immunoelectroassay.⁷⁾ Willebrand factor (VIII:WF) was measured by the method of Weiss *et al.*⁸⁾ Platelet aggregation with ristocetin (Lundbeck) was measured using an aggregometer (Bryston, USA) at the concentration of 1.25 mg/ml. The endothelial cells derived from an umbilical cord vein were cultured for 72 hours according to the method of Jaffe *et al.*⁹⁾ Cultured cells were observed by an indirect immunofluorescent antibody technique using heterologous anti-factor VIII antibody.¹⁰⁾

Factor VIII activities of 15 normal pregnant women at the third trimester and 14 non-pregnant, mismatched women were assayed.

CASE REPORT

K. K., a 24-year-old woman (gravida 0, para 0) came to the out-patient clinic of Niigata University Hospital on Nov. 6, 1972 for examination of a bleeding disorder. The patient gave a history of having had frequent epistaxis and profound bleeding after a tooth extraction during childhood and after appendectomy at the age of 14. But she denied having menorrhagia, metrorrhagia and hemarthrosis. There was no consanguinity in her family. As shown in the pedigree of the family (Fig. 1), she had two sisters (III-1, 2) and a brother (III-3, proband) and they have had similar bleeding diathesis. As shown in Table, the coagulation studies revealed that the patient (III-4) had normal platelet count, prolonged bleeding time (26 min), prolonged A-PTT (52.7 sec), decreased platelet retention rate, absence of ristocetin-induced platelet aggregation and low levels of factor VIII biological properties (VIII: C 38%, VIII: AG 22% and VIII: WF 20%) and that the patient, her two sisters and brother all had vWD. Her father showed negative results, although her mother was not examined. A plasma infusion test confirmed the diagnosis of vWD in which 490 ml of fresh frozen plasma (10 ml/kg) was infused into the patient (Fig. 2). Infusion of normal plasma produced a sustained rise of VIII: C greater than the expected level. VIII: WF response was parallel with that of VIII: C, but VIII: AG increased gradually. Bleeding time was shortened from 22 min to 6 min.

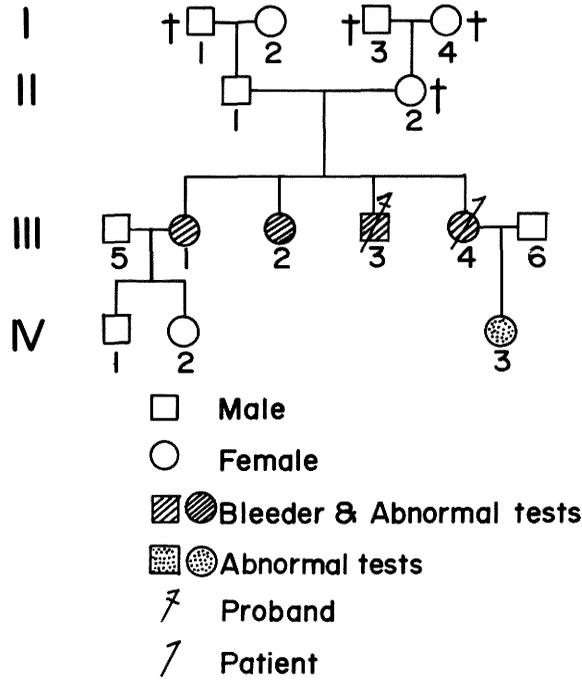


Fig. 1. Pedigree

Table Coagulation studies in the family.

	II-1	II-2	III-1	III-2	III-3	III-4	III-6	IV-1	Normal range
	Father	Mother	Sister	Sister	Broth.	Pat.	Husb.	Baby	
Age	58	54†	33	29	27	24	27	0	
Sex	M	F	F	F	M	F	M	F	
Platelet count ($\times 10^4/mm^3$)	354	—	44.1	28.7	29.3	260	27.0	—	13-30
Bleeding time (min)	3.0	—	31.0	>30	11.5	26.0	5.0	3.0	1-5
A-PTT(sec)	35.4	—	52.0	48.2	45.0	52.7	35.4	—	30-40
Factor VIII									
VIII _{AHF} (%)	100	—	36	36	66	38	90	—	46-190
VIII _{AGN} (%)	—	—	65	65	100	22	100	70	66-105
VIII _{VWF} (%)	—	—	54	50	13	20	82	36	56-140
Ristocetin test (1.25 mg/ml) (%)	—	—	4	3	6	3	—	—	70-100
Platelet retention rate (%)	—	—	29.5	13.8	29.1	22.7	35.6	—	48-86
Plasma infusion test	—	—	—	—	(+)	(+)	—	—	
Hemorrhagic diathesis	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	

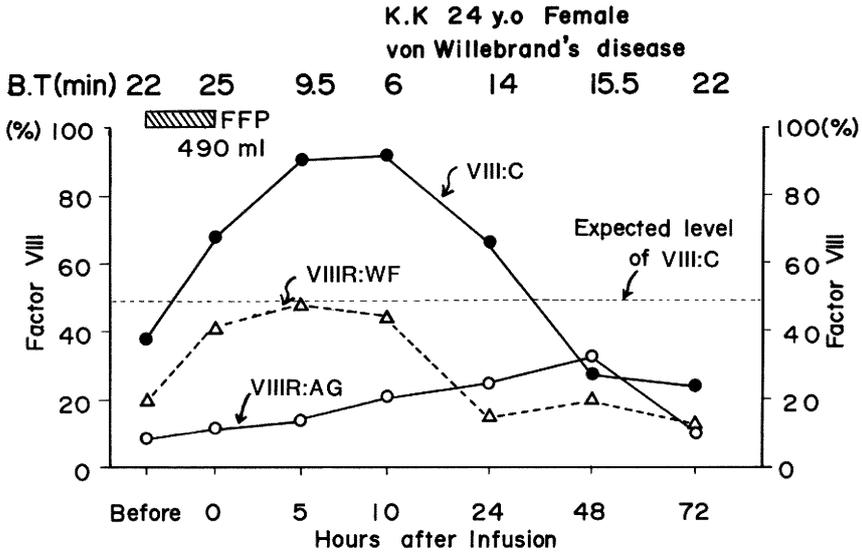


Fig. 2. Plasma infusion test

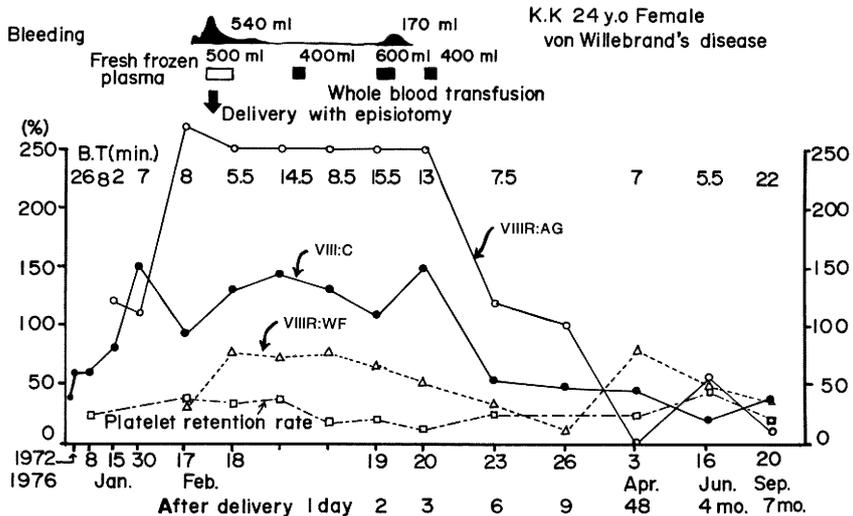


Fig. 3. Clinical course.

The patient visited the out-patient clinic of the Department of Obstetrics, complaining of emesis and amenorrhea on July 7, 1975. Her last menstruation started on May 12, 1975. Obstetrical examination revealed a normal gravid uterus, two months advanced. She was checked hematologically at periodic intervals starting after 9 months of pregnancy. During the third trimester of pregnancy, bleeding time was shortened, VIII: C and VIII R: AG were gradually increased. However, platelet retention rate and VIII R: WF were not normalized. The patient was admitted to the Department of Obstetrics of

Niigata University Hospital, complaining of labor on Feb. 17, 1976. Fig. 3 shows the clinical course and the results of the coagulation studies of the patient before and after delivery. The hematological findings of the patient at the expected date of confinement (on Feb. 17, 1976) were as follows: bleeding time 8.0 min, A-PTT 44.4 sec, platelet retention rate 33.4%, VIII: C 92%, VIIIIR: AG 200% and VIIIIR: WF 30%. The discrepancy of factor VIII between VIIIIR: WF and VIII: C or VIIIIR: AG is noteworthy. The patient delivered a female infant weighing 3,220 g on Feb. 18, 1976. The prophylactic infusion of 500 ml of fresh frozen plasma was performed immediately before delivery. Right medio-lateral episiotomy was also performed. The contraction of the uterus was fairly poor, so uterine massage and injection of uterus-contracting drugs were given. Blood loss during delivery was 440 ml (at the first stage; 0 ml, at the second stage; 20 ml and at the third stage; 420 ml) and postpartum blood loss was 270 ml. Blood loss during delivery was within the normal range (less than 500 ml). Stored whole blood (1,400 ml) was infused after delivery to improve anemia. The patient and her baby had no bleeding troubles throughout the course of delivery. VIII: C and VIIIIR: WF were increased to 150% and 80%, respectively, immediately after delivery, and then gradually dropped to the level before pregnancy. VIIIIR: AG remained at the markedly high level of 250% until the third postpartum day, then gradually dropped to the level before pregnancy. Bleeding time and platelet retention rate remained slightly abnormal. The postpartum course was uneventful and the patient was discharged on the tenth postpartum day. As shown in Table, VIIIIR: AG and VIIIIR: WF of the cord blood of the baby (IV-1) were 70% and 36%, respectively. As for the diagnosis of the baby, vWD was probable because of decreased VIIIIR: WF, despite normal VIIIIR: WF and bleeding time. Furthermore, we

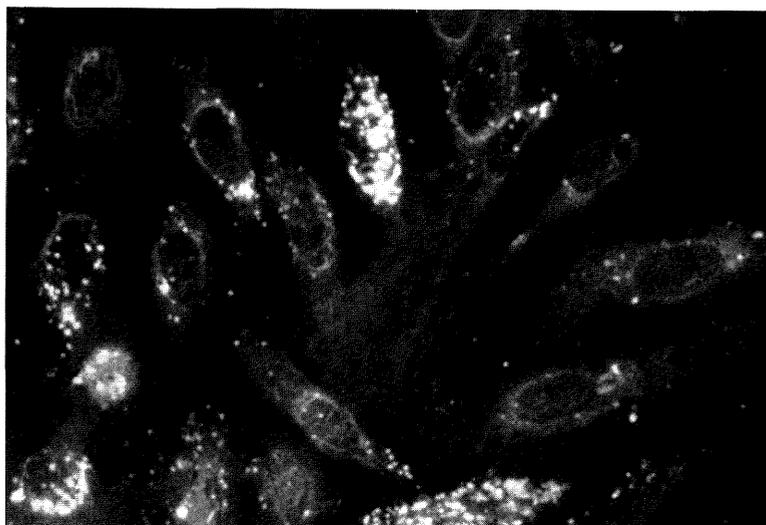


Fig. 4. Localization of factor VIII-related antigen in cultured endothelial cells derived from umbilical cord vein of the baby by indirect fluorescent antibody technique. $\times 200$

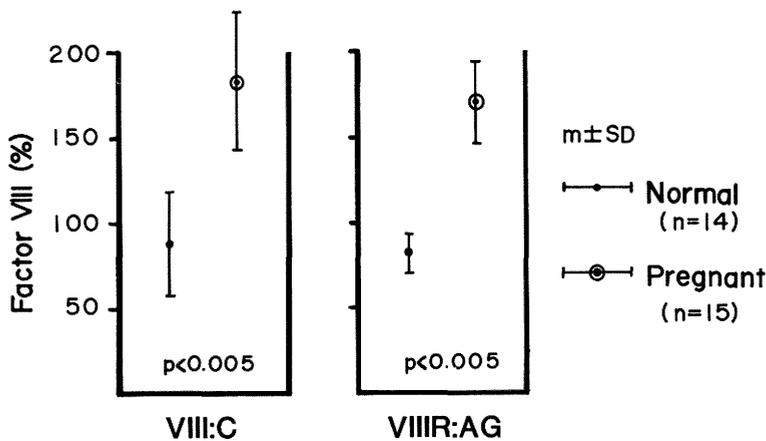


Fig. 5. Factor VIII activities in pregnant and non-pregnant women.

had a chance to culture endothelial cells derived from the umbilical cord vein of the baby. Localization of factor VIII-related antigen was demonstrated in the cytoplasm of cultured endothelial cells by indirect immunofluorescent antibody technique, as shown in Fig. 4.

The pattern of localization of factor VIII-related antigen was granular and similar to that of normal subjects. The averages of two biological properties of factor VIII in 15 pregnant women were VIII: C: $184 \pm 40\%$ and VIII R: AG: $71 \pm 24\%$, compared with those of VIII: C: $87 \pm 31\%$ and VIII R: AG: $82 \pm 12\%$ in non-pregnant women, as shown in Fig. 5. VIII: C and VIII R: AG were significantly increased in pregnant women ($P < 0.0005$).

DISCUSSION

It is generally accepted that the hemostatic abnormalities of vWD often improve during pregnancy.¹¹⁾ However, very little data have been published concerning the management of pregnant patients with vWD.

We have presented here a case of a pregnant woman with vWD who delivered a female infant without bleeding trouble. Our case had been diagnosed as mild vWD because of prolonged bleeding time, decreased platelet retention rate, absence of aggregation with ristocetin, low level of factor VIII and "overresponse" of factor VIII coagulant activity to infusion of normal plasma. Hemostatic abnormalities including bleeding time, activated PTT and factor VIII (VIII: C and VIII R: AG) improved during pregnancy, except for platelet retention rate and VIII R: WF.

Previous studies have shown that the levels of several coagulation factors, particularly fibrinogen, prothrombin, factor VII, factor VIII, factor X and factor IX, are increased during pregnancy in healthy women and female patient with vWD.^{11),12)} However, platelets seem little affected by pregnancy.^{11),11)} Winckelman *et al*¹³⁾ showed

that the average level of factor VIII coagulant activity was 246% ($\pm 108\%$ S. D.) in 25 pregnant females, compared with 102% ($\pm 175\%$) in 25 different women. Preston¹⁴⁾ reported that the average level was 223% in 27 patients immediately after delivery, compared with 158% in 7 patients immediately before labor. Similar findings were reported by others.^{12),15)}

Our case showed decreased platelet retention rate and VIII: WF before delivery. Similar cases were reported by others.^{15),16),17),18)}

It is reported that factor VIII is rapidly increased after delivery because stress due to operation, labor and delivery possibly induce the release of adrenalin,^{10),16),20),21)} which has a capacity to release factor VIII from the vascular intima.

We also confirmed that factor VIII activities (VIII: C and VIII: AG) were increased in 15 pregnant women at the third trimester. However, factor VIII declined to low levels soon after delivery. Therefore, abortion or premature delivery may be complicated by severe hemorrhage even though the same patient may previously have delivered at the end of third trimester without incident.¹⁰⁾

It is also well known that some stresses and chemical agents may release factor VIII and plasminogen activators from the vascular wall.^{20),21),22),23),24),25)}

Although we had noticed that this case had normal VIII: C and VIII: AG and subnormal bleeding time before delivery, we infused fresh frozen plasma immediately before delivery prophylactically because we had never experienced such a case before.

The prophylactic use of factor VIII preparations during pregnancy or at delivery in patients with vWD is controversial.^{2),18),27)} Many reports^{2),10),27),29),30)} indicate that vaginal delivery is safe in patients with vWD when factor VIII coagulant activity is elevated just before delivery. Caesarean section may be also accomplished safely with or without prophylactic use of factor VIII preparations.^{2),10),16)} However, in some deliveries with obstetrical-gynecological complications, such as abortion or premature separation of placenta,¹⁷⁾ serious bleeding troubles have been encountered during pregnancy, especially in severe cases.^{2),28)}

In retrospect, we now consider that the prophylactic use of fresh frozen plasma might have been unnecessary as suggested by some obstetricians,^{2),16),27)} because this patient had a mild form of vWD and had planned to deliver vaginally, and factor VIII coagulant activity was elevated just before delivery. Moreover, episiotomy is minor surgery and the use of factor VIII preparations always carries the risk of allergic reaction and serum hepatitis.

The prophylactic use of factor VIII preparations at delivery of patients with mild or moderate vWD is unnecessary when factor VIII coagulant activity is elevated (more than 50%).²⁹⁾

Localization of VIII: AG in the cytoplasm of cultured endothelial cells derived from the umbilical cord vein of the baby shows that the baby has mild von Willebrand's disease and the endothelial cells of the baby can synthesize VIII: AG.

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