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von Willebrand Disease and Women's Health

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In 1926 von Willebrand described a bleeder family in Aland; this condition became known as von Willebrand disease (VWD). von Willebrand noted that "the trait seemed especially to be seen among the women." Today, the use of a pictorial bleeding assessment chart (PBAC) has enabled the prevalence of VWD to be established among women presenting with menorrhagia, as well as the documentation of this symptom in women with known VWD and the assessment of treatment response in menorrhagia. Treatments for menorrhagia include tranexamic acid, desmopressin (DDAVP) administered either intranasally or subcutaneously, the oral contraceptive pill, the "Mirena" coil (Schering Oy, Turku, Finland), and endometrial ablation. Von Willebrand factor (VWF) shows strong cyclical variation, with peak values occurring in the luteal phase. Although increased in pregnancy, levels of VWF decline postnatally and the incidence of both primary and secondary postpartum hemorrhage is high (20% to 25%). Baseline VWF levels less than 15 IU/dL are unlikely to reach greater than 50 IU/dL in the third trimester, and therefore prophylaxis with DDAVP or VWF-containing concentrate to cover delivery should be considered.
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In 1926 von Willebrand described 66 members of a bleeder family in Aland and noted that 16 of 35 women had the trait, but only seven of 31 men. Thus von Willebrand made the observation "the trait seemed especially to be seen among the women." He stated that "in the female bleeders, the diathesis becomes manifest both in a milder and a graver form, whereas the males show only the mild form. Among the female members, five deaths from bleeding have occurred"[1] (Fig 1). The index case, Hjordis, was 5 years old when first examined and experienced several severe episodes of bleeding from the nose and lips. Her mother, Mrs S, had frequent and persistent nose bleeding during her entire youth and her menstruation had always been copious. However, her deliveries had been normal without heavy bleeding. Hjordis was one of 12 siblings. It is notable that the maternal grandmother of Mrs Augusta S had bled to death in childbirth.

Thus in his paper, von Willebrand stated that for women, "genital hemorrhage" in connection with menstruation and delivery is the second most common cause of bleeding. However, he also made the point that menstruation and delivery might be completely normal.

In 1957 Nilsson et al described 13 members of 10 families who had severe bleeding disorders characterized by factor VIII deficiency and a prolonged bleeding time.[2] One of these 13 patients was Birgitta, who had experienced severe bleeding from the gums and nose since early childhood and presented age 15 years with life-threatening uterine bleeding. At that time the Blombacks were working on a method of purifying fibrinogen using Cohn's fraction 1. This fraction 1 − 0 was used for the first time for the treatment of Birgitta[3] (Fig 2).

Menorrhagia and von Willebrand's Disease

A 1981-82 study by the Royal College of General Practitioners (RCGP) from the United Kingdom showed that 5% of women aged 30 to 49 years consulted their physician for menorrhagia.[4] A study of patterns of referral in 1992 showed that 12% of gynecology referrals were for menorrhagia.[5] However, although menorrhagia is a common complaint, patient history alone is a very poor indicator of true menorrhagia. Menorrhagia is defined subjectively as excessive or prolonged loss of blood on a regular cyclical basis, or objectively as greater than 80 mL blood loss for the whole period.[6]

Higham et al compared two methods of assessing menstrual blood loss: a pictorial assessment chart (PBAC)[7] and the alkaline hematin method[8] (Fig 3). The scores assigned were 1 for each lightly stained tampon, 5 if moderately soiled, and 10 if completely saturated with blood. Towels were given ascending scores of 1, 5, and 20 and small and large clots scored 1 and 5, respectively. A score greater than 100 was

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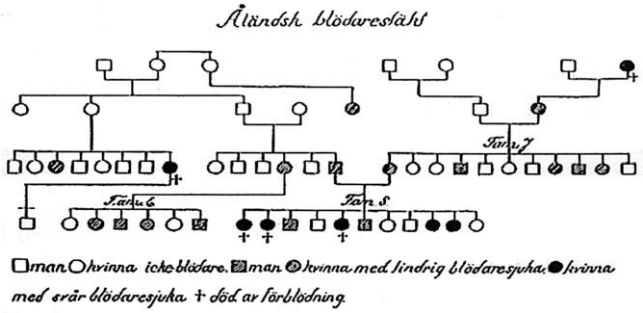

Figure 1 The original family described by von Willebrand.[1]

defined as menorrhagia and was equivalent to a greater than 80-mL blood loss.

Frequency of VWD in Women With Menorrhagia

Kadir et al assessed the frequency of VWD in a gynecology clinic.[9] All patients referred to the gynecology clinics at the Royal Free Hospital, London, between October 1995 and June 1997 with a history of heavy, regular (every 23 to 39 days) bleeding were eligible. A menstrual and bleeding history was taken. Each patient completed the PBAC, and only the 150 sequential patients scoring greater than 100 were assessed further. Activated partial thromboplastin time (aPTT), factor VIII (FVIII) activity, von Willebrand factor antigen (VWF:Ag) and activity (VWF:AC), and factor XI (FXI) were measured in all patients. (FXI was measured because of the significant Jewish population in the local catchment area.) Of the 150 women tested, 15 had VWD of mild severity and three of moderate severity (Fig 4).

The demographic details of the patients with VWD are shown in Tables 1 and 2. A particularly significant feature was that more women with VWD had menorrhagia since the menarche compared to women without a bleeding disorder. The frequency of other bleeding symptoms was also higher in patients with VWD than in women without a bleeding disorder. Easy bruising, bleeding after tooth extraction, and postpartum and postoperative bleeding were all more common in patients with VWD. The study concluded that patients with menorrhagia and without obvious pelvic anomalies should be tested for VWD, and emphasized the importance of a careful medical history because of the highly predictive factors: menorrhagia from the menarche, and a history of bleeding after tooth extraction, surgery, or parturition.

More recently, there has been a systematic review of VWD in women with menorrhagia.[10] Eleven studies were included, totaling 988 women with menorrhagia. The prevalence of VWD ranged from 5% to 24% in individual studies, and a total of 131 (13%) women were diagnosed with VWD. The prevalence was higher in the European studies (18%; 95% confidence interval [CI], 15% to 23%) compared with that in North American studies (10%; 95% CI, 7.5% to 13%) (Fig 5). This variation was likely the result of differences in the studies, including the method of recruitment of the study population, the method of assessing menstrual blood loss, the ethnic composition of the study population, the criteria for diagnosis, and the use of race- and ABO group–specific values for VWF.[11-19]

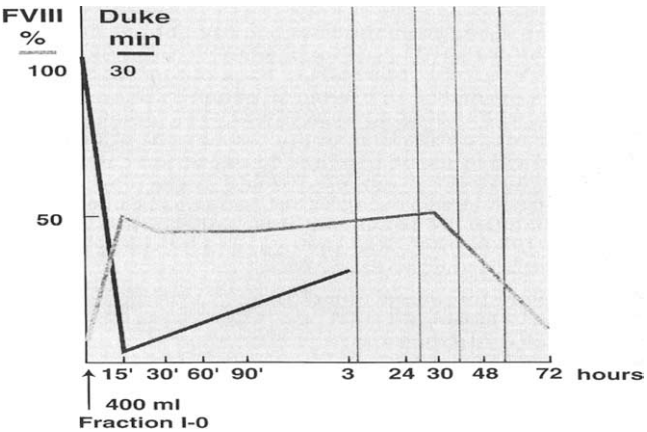

Figure 2 The effect of administration of fraction 1.0 to a patient with severe von Willebrand disease. Reprinted from Nilsson et al[3] with permission of Blackwell Publishing Ltd.

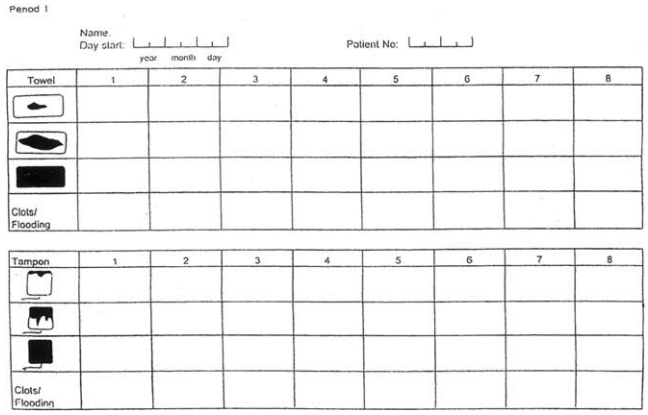

Figure 3 The pictorial bleeding assessment chart. Reprinted from Higham et al[7] with permission of Blackwell Publishing Ltd.

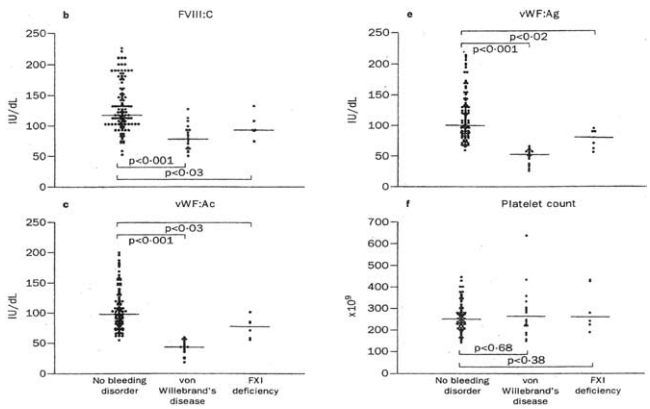

Figure 4 Scatter plots of coagulation markers in women with menorrhea. Reprinted with permission from Elsevier (*The Lancet*, 1998, 351:485-489).[9]

Table 1 Demographic Features and Details of Menstrual History

	Total (N = 150)	No Bleeding Disorders (n = 123)	von Willebrand's Disease (n = 20)	P
Bleeding symptoms				
Bruising	88 (58.7%)	66 (53.7%)	16 (80%)	.05
Nose bleeding	22 (14.7%)	17 (13.8%)	5 (25.0%)	.20
Gum bleeding	54 (36%)	41 (33.3%)	9 (45.0%)	.45
Bleeding after tooth extraction*	13/98 (13.3%)	6/81 (7.4%)	6/13 (46.2%)	.001
Postoperative bleeding*	18/109 (16.5%)	7/90 (7.8%)	8/13 (61.5%)	<.001
Postpartum bleeding*	29/27 (29.9%)	417/80 (21.3%)	8/13 (61.5%)	.005
Symptom score				
0	40 (26.7%)	39 (31.7%)	0	
1–2	78 (52.0%)	65 (52.9%)	11 (55.0%)	
3–4	28 (18.7%)	17 (13.8%)	7 (35.0%)	
5–6	4 (2.7%)	2 (1.6%)	2 (10.0%)	<.001
Median (range)	1 (0–5)	1 (0–5)	2 (1–5)	<.001

*Expressed as a percentage of women who had the event or procedure.
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It has been demonstrated that menorrhagia is a common symptom in women with previously identified VWD. In 66 women with VWD surveyed using the PBAC, menorrhagia was confirmed in 74% compared with 29% in an age-matched control group[20] (Fig 6). Furthermore, in this survey five of 66 women with VWD required hysterectomy, and one woman had secondary postoperative bleeding requiring blood transfusion despite prophylaxis. In Iran, type 3 VWD is more common in rural areas where consanguineous marriages are common. The national registry of inherited coagulation disorders lists 600 patients and therefore a prevalence of 60 per million, in contrast to the UK prevalence of one per million.[21] Lak et al studied 385 patients, including 182 women with type 3 VWD, and found 90 of 130 (69%) expe-

Table 2 Other Bleeding Symptoms and Symptom Scores

	All Patients (N = 150)	No Bleeding Disorders (n = 123)	von Willebrand's Disease (n = 20)	P
Median age, Yr (range)	39 (15–50)	39 (15–50)	40 (27–50)	.83
Hemoglobin <110 g/L	22 (14.7%)	19 (15.5%)	2 (10.0%)	.74
Blood group				
A	58 (38.7%)	49 (39.8%)	6 (30.0%)	
O	62 (41.3%)	48 (39.0%)	11 (55.0%)	
Others	30 (20.0%)	26 (21.1%)	3 (15.0%)	.40
Family history of bleeding disorder	4 (2.7%)	2 (1.6%)	1 (5.0%)	.37
History of blood transfusion	17 (11.3%)	10 (8.1%)	3 (15.0%)	.39
Duration of menorrhagia				
<24 mo	61 (40.7%)	57 (46.3%)	3 (15.0%)	
>24 mo	62 (41.3%)	55 (44.7%)	4 (20.0%)	
Since menarche	27 (18.0%)	11 (8.9%)	13 (65.0%)	.001
Duration of menstruation				
Median, days (range)	6.5 (3–13)	6.5 (3–13)	6.5 (5–12)	.36
Passage of clots	131 (87.9%)	107 (87.7%)	17 (85.0%)	.72
Episodes of flooding	106 (70.7%)	84 (63.3%)	16 (80.0%)	.43
Median PBAC score (range)	184 (100–1036)	172 (100–667)	297 (122–800)	<.001

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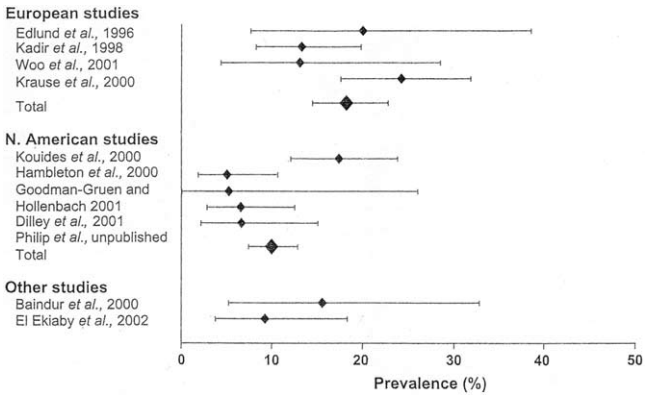


Figure 5 Prevalence rates of VWD in women with menorrhagia. Reprinted from Shankar et al[10] with permission of Blackwell Publishing Ltd.

rienced menorrhagia. Menorrhagia was not evaluated objectively and therefore the prevalence could have been higher.

The effect of ABO blood group on VWF is well known and it has been specifically demonstrated in hemophilia carriers and normal women that FVIII:C and VWF:Ag are lower in women with blood group O.[22,23] More recently, the variation of coagulation factors in women was assessed in a cross-sectional study of 123 women that assessed the effect of age, ethnic origin, blood group, and menstrual cycle on the aPTT, FVIII:C, VWF:Ag, and VWF:AC.[24] The aPTT was longer in women with blood groups B or O, and plasma levels of FVIII:C, VWF:Ag, and VWF:AC were significantly higher in black women. The effect of the menstrual cycle on VWF levels was further assessed in a longitudinal study of 39 Caucasian women, 20 of whom were taking a combined oral contraceptive. VWF:Ag and VWF:AC showed strong cyclical variation with peak values in the luteal phase. This pattern was dampened for VWF:Ag and VWF:AC with use of the

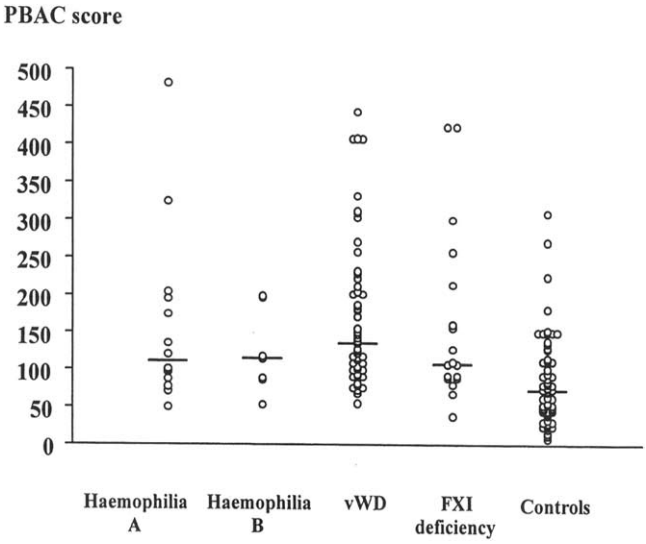
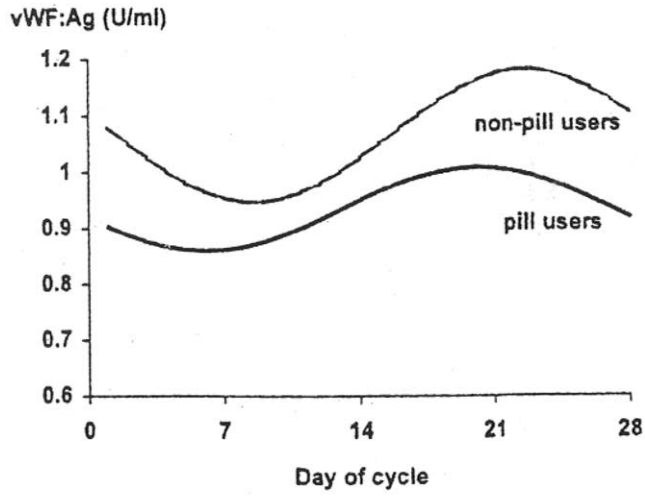


Figure 6 Menstrual scores in carriers of hemophilia A, hemophilia B, patients with VWD, patients with FXI deficiency, and controls. Reprinted from Kadir et al[20] with permission of Blackwell Publishing.



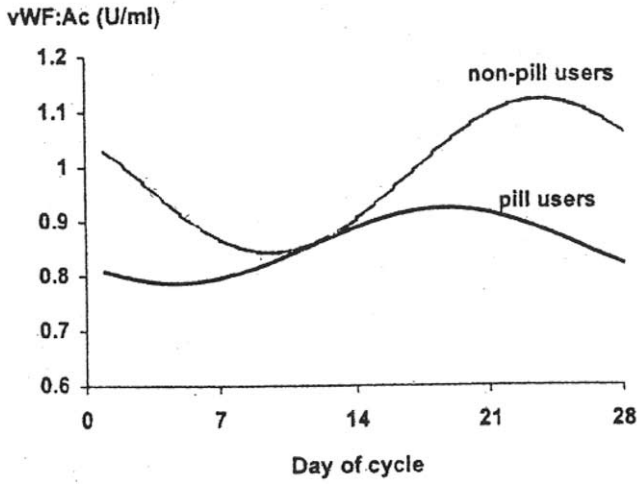


Figure 7 Variation of VWF during the menstrual cycle. Reprinted from Kadir et al[24] with permission of Schattauer GmbH.

contraceptive pill (Fig 7). A number of longitudinal studies on the variation of coagulation factors in the menstrual cycle have produced conflicting results,[25-30] possibly due to the small numbers of women in these studies and the statistical methods used. The wide inter- and intraindividual variation in these factor levels means that real differences between the different phases of the menstrual cycle may be missed unless large groups of women are studied using approaches that take account of the large variation between individuals. In the longitudinal study of Kadir et al changes over time were studied using multilevel modeling methods. Thus, as most female hormones are at a baseline in the early follicular phase (no later than day 7 of the cycle) blood sampling for assessment of clotting factors during this phase is recommended. It is also important to avoid planned surgical intervention during the early follicular phase in patients with mild VWD.

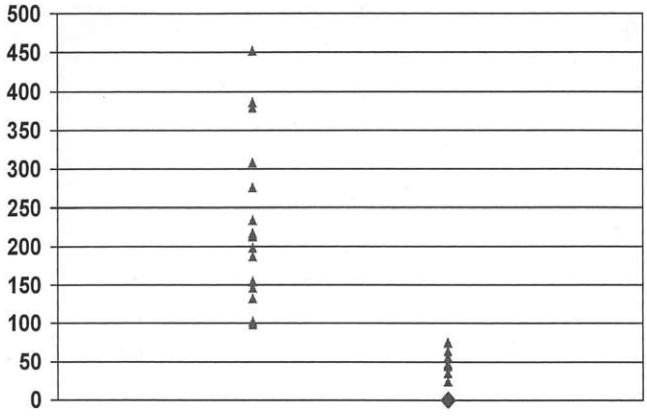


Figure 8 Pictorial bleeding assessment chart score pre- and postinsertion of the levonorgestrel-releasing intrauterine system. Reprinted from Kingman et al[34] with permission of Blackwell Publishing.

Management of Menorrhagia in Women With VWD

The most widely used medical treatment for women with menorrhagia and VWD is antifibrinolytics, in particular tranexamic acid. In a randomized control trial, tranexamic acid reduced menstrual blood loss by 54% when given in a dose of 1 g every 6 to 8 hours.[31] There is an anecdotal report of high-dose tranexamic acid administered as a single daily 4-g dose.[32] However, the side effects of headache and gastrointestinal disturbance may preclude the use of such a high dose.

Although the Cochrane database does not recognize oral contraceptive as effective therapy for menorrhagia, there are reports showing its efficacy in VWD. Thus, according to an International Society of Thrombosis and Hemostais (ISTH) survey of 40 women with type 2 or type 3 VWD, it was 80% effective.[33] More recently, the levonorgestrel-releasing intrauterine system (Mirena; Schering Oy, Turku, Finland) has been used to control menorrhagia in VWD.[34] The Mirena coil has been shown to reduce menstrual blood loss by 74% and 97% at 3 and 12 months in women with menorrhagia and normal coagulation, with minimal side effects.[35] Sixteen women with inherited coagulopathy, including 13 with VWD, were followed for up to 9 months following Mirena insertion.[34] Prior to insertion, all women had high PBAC scores (median, 213; range, 98 to 386); following insertion, the median score was 47 with a range of 24 to 75 ($P = .0001$) (Fig 8). The Mirena system was originally developed as a contraceptive but it is increasingly useful as a medical treatment of menorrhagia. It acts by suppressing growth of the endometrium and spiral arterioles, as well as increasing capillary thrombosis. Provided women with a coagulopathy are adequately treated for the bleeding disorders at the time of insertion, there should be no risk of excessive bleeding.

Intranasal desmopressin (DDAVP) increases plasma levels of FVIII and VWF in VWD.[36] In a cohort study of intranasal DDAVP with 721 daily uses in 90 women, the subjective response was excellent in 64% and good in 28%; there was no response in 8%.[37] A randomized, placebo-controlled cross-over trial of nasal DDAVP showed that menstrual blood loss was less heavy in VWD; however, this was not statistically significant, probably due to the small sample size.[38] A prospective multicenter study of subcutaneous DDAVP in women with VWD or nonsevere hemophilia A showed effectiveness 86% of the time and no effect 14% of the time.[39] Although most women tolerate DDAVP with few side effects, it is important to have strict fluid restriction in order to avoid hyponatremia.

Endometrial ablation is increasingly being used in the general population as a treatment for menorrhagia. This was assessed in a consecutive series of seven patients with VWD in Rochester, NY.[40] Three patients underwent endomyometrial resection and one each underwent rollerball, thermal, electrocautery, and balloon ablation. All patients were pretreated with DDAVP, apart from one patient with type 2A VWD who was given clotting factor concentrate. Although all patients initially responded (two amenorrhea, four hypomenorrhea, one moderate improvement) and all quality-of-life assessments showed significant improvement at a median of 11 months postablation, four patients had recurrence of menorrhagia and three required hysterectomy. It was concluded from this case series that endometrial ablation is a safe procedure in VWD but that the long-term efficacy seems less than in women without VWD.

In a retrospective review of 66 of 118 women with VWD who responded to a questionnaire, five (8%) had required a hysterectomy for menorrhagia and two experienced postoperative hematoma.[41] Clearly, the successful management of such procedures requires close cooperation between the gynecologist, anesthetist, and hematologist. However, it is important to remember that excessive bleeding can be surgical and is not always the result of inadequate replacement therapy.

Pregnancy and von Willebrand Disease

The physiologic response to pregnancy is the elevation of FVIII and VWF[42,43] (Fig 9). Thus women with VWD mostly do not bleed during pregnancy. A review of 84 pregnancies from 1980 to 1996 of women with VWD showed that 28 of 84 (33%) threatened spontaneous miscarriage in the first trimester; however, only 18 (21%) had a spontaneous miscarriage, which is no different from the normal rate of 16%.[43] Women with VWD may present earlier than other women if they experience bleeding in early pregnancy.

If the VWF level is not normalized, the use of DDAVP may be considered. This is controversial because of concerns regarding a vasoconstrictive effect on placental flow, the risk of premature labor due to the potential oxytoxic effects of DDAVP,[44,45] and the risk of maternal and neonatal hyponatremia.[46] There is a view that DDAVP is safe to use in the antepartum period and no adverse effect was seen in the

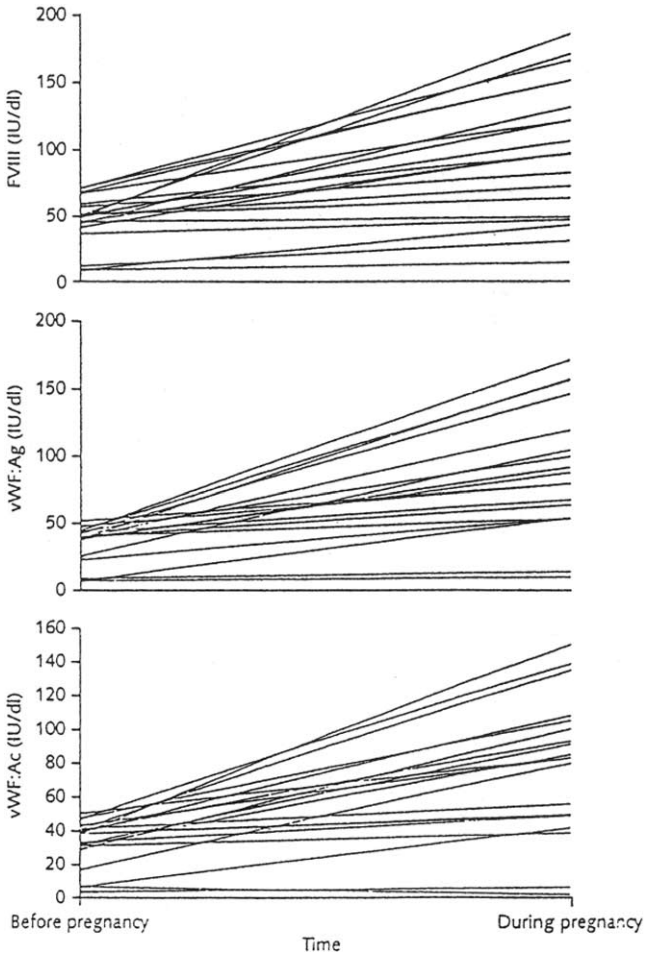


Figure 9 Levels of FVIIIC, VWF:Ag and VWF:AC during pregnancy. Reproduced from Kadir et al,[43] with permission of the Royal College of Obstetricians and Gynaecologists.

second trimester when 31 women with VWD underwent chorionic villus sampling.[47]

In a large series of 24 pregnancies in 13 women with VWD studied retrospectively in pregnancy, it was noted that FVIII:C and VWF:Ag rose 1.5-fold during gestation in most cases.[48] However, a baseline FVIII:C of less than 15 IU/dL (4/14 cases) was predictive of a level in the third trimester of less than 50 IU/dL; improvements of VWF were less marked. In those patients with serial data, a baseline level less than 15 IU/dL did not reach a VWF level greater than 50 IU/dL in the third trimester. Thus, in the management of pregnancy, it is important to document the VWF level in the third trimester. In order to avoid postpartum hemorrhage, it may be necessary to give prophylaxis with a clotting factor concentrate containing VWF.

Several studies have shown that there is an increase in postpartum hemorrhage in pregnancy defined as greater than 500 mL blood loss in the first 24 hours after delivery (primary) and excess of normal lochia 24 hours to 6 weeks postnatally (secondary).[43,48,49] Thus the risk of primary postpartum hemorrhage in women with type 2 VWD who did not receive prophylaxis with concentrate containing VWF was 37.5% (three of eight deliveries). The overall incidences of primary and secondary postpartum hemorrhage were 15.8% and 25%, respectively.[48]

The overall risk of secondary postpartum hemorrhage may be less well appreciated. The accepted risk in normal individuals is 1.3%.[50] One problem is the variable decline of VWF levels to baseline levels after delivery. There are anecdotal reports of a 7-day decrease from 41 IU/dL to 9 IU/dL[48] and a fall to half values within 6 hours postdelivery.[51] Thus it is important for patients to report excessive bleeding on discharge home, and for hemoglobin levels in the postnatal period to be documented.

In areas of the world where type 3 VWD is more common, it is important to provide adequate therapy in the postnatal period. A study from Iran noted a postpartum hemorrhage rate of 15% (15 of 100 women) and that abnormal bleeding usually occurred when treatment was suboptimal in dosage or given for too short a time (1 day instead of 3 to 4 days).[21]

To provide a dedicated and comprehensive obstetric and gynecological service for women with bleeding disorders, it is important to provide a multidisciplinary clinic with a consultant obstetrician and gynecologist with an interest in coagulopathies, a consultant hematologist, and specialist hemophilia nurse. During the first year of operation of such a clinic 29% (27 of 90) women had VWD.[52] Such a clinic increases awareness of the special needs of women with VWD in the local community, which is particularly important for such a common bleeding disorder, with a reported prevalence of 1%.[53]

References

1. von Willebrand EA: Hereditar pseudohemofili. Finska Lakarsallskapets Handl 67:7-112, 1926
2. Nilsson IM, Blomback M, von Francken I: On an inherited autosomal hemorrhagic diathesis with antihemofiliglobulin (AHG) deficiency and prolonged bleeding time. Acta Med Scand 159:35-57, 1957
3. Nilsson IM, Blomback M, Blomback B: v. Willebrand's disease in Sweden. Its pathogenesis and treatment. Acta Med Scand 164:263-278, 1959
4. Royal College of General Practitioners, Office of Population Censuses and Surveys, Department of Health and Social Security: Morbidity Statistics From General Practice. Third National Study 1981-1982. Series MBS no.1. London, UK, HMSO, 1986
5. Bradlow J, Coulter A, Brooks P: Patterns of Referral. Oxford, UK, Health Service Research Unit, 1992
6. Hallberg I, Hogdahl AM, Nilsson L, Rybo G: Menstrual blood loss–A population study. Acta Obstet Gynecol Scand 45:320-351, 1996
7. Higham JM, O'Brien PMS, Shaw RW: Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 97:734-739, 1990
8. Hallberg L, Nilsson L: Determination of menstrual blood loss. Scand J Clin Lab Invest 16:244-248, 1964
9. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA: Frequency of inherited bleeding disorders in women with menorrhagia. Lancet 351: 485-489, 1998
10. Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA: von Willebrand disease in women with menorrhagia: A systematic review. Br J Obstet Gynaecol 111:734-740, 2004
11. Edlund M, Blomback M, von Schoultz B, Anderrson O: On the value of menorrhagia as a predictor of coagulation disorders. Am J Hematol 53:234-238, 1996
12. Woo YL, White B, Corbally M, Byrne M, O'Connell D, O'Shea E, et al: Von Willebrand's disease: An important cause of dysfunctional bleeding. Blood Coagul Fibrinolysis 13:89-92, 2002
13. Krause M, Aygoren-Pursun E, Ehrenforth S, Ludwig G, Vigh TH, Schar-

rer I: Coagulation disorders in women with menorrhagia. Haemophilia 6:240-247, 2000
14. Kouides P, Phatak P, Sham R, Braggins C, Tara M, Cox C, et al: The prevalence of subnormal von Willebrand factor levels in menorrhagia patients in Rochester, NY: A final analysis. Haemophilia 6:244, 2000
15. Hambleton J, Roth J, Jurnack-Dewell J, Schwartz B, Seremetis S: Prevalence of unrecognized von Willebrand disease in women with menorrhagia: A preliminary report. Haemophilia 6:242, 2000
16. Goodman-Gruen D, Hollenbach K: The prevalence of von Willebrand disease in women with abnormal uterine bleeding. J Women's Health Gender Based Med 10:677-680, 2001
17. Dilley A, Drews C, Miller C, Lally C, Austin H, Ramaswamy D, et al: von Willebrand disease and other inherited bleeding disorders in women with diagnosed menorrhagia. Obstet Gynecol 97:630-636, 2001
18. Baindur S, Shetty S, Pathare AV, Salvi V, Ghosh K, Mohanty D: Screening for von Willebrand disease in patients with menorrhagia. Haemophilia 6:240-241, 2000
19. El Ekiaby M, Ahmed A, Farag O, Khattab D: von Willebrand disease as a cause of menorrhagia. Haemophilia 8:512-514, 2002
20. Kadir RA, Economides DL, Sabin CA, Pollard D, Lee CA: Assessment of menstrual blood loss and gynaecological problems in patients with inherited bleeding disorders. Haemophilia 5:40-48, 1999
21. Lak M, Peyvandi F, Mannucci PM: Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 Willebrand disease. Br J Haematol 111:1236-1239, 2000
22. Wahlberg TB, Savidge GF, Blomback M, Wiechel B: Influence of age, sex and blood groups on blood coagulation laboratory variables in a reference material composed of 80 blood donors. Vox Sang 39:301-308, 1980
23. Graham JB, Rizza CR, Chediak J, Mannucci PM, Briet E, Ljung R, et al: Carrier detection in haemophilia A: A cooperative international study. The carrier phenotype. Blood 67:1554-1559, 1986
24. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA: Variations in coagulation factors in women: Effects of age, ethnicity, menstrual cycle and combined oral contraceptive. Thromb Haemost 82:1456-1461, 1999
25. Mandalaki T, Louizou C, Dimitriadou C, Symeonidis P: Variations in factor VIII during the menstrual cycle in normal women. N Engl J Med 302:1093-1094, 1980
26. Cederblad G, Hahn L, Korsan-Bengtsen K, Pehrsson NG, Rybo G: Variations in blood coagulation, fibrinolysis, platelet function and various plasma proteins during the menstrual cycle. Haemostasis 6:294-302, 1977
27. Jespersen J: Sequential study of plasma euglobulin fibrinolytic activity during the normal menstrual cycle and in women on oral contraceptives low in estrogen. Gynecol Obstet Invest 15:266-274, 1983
28. Siegbahn A, Odlind V, Hedner U, Venge P: Coagulation and fibrinolysis during the normal menstrual cycle. Ups J Med Sci 94:137-152, 1989
29. Lebech AM, Kjaer A: Lipid metabolism and coagulation during the normal menstrual cycle. Horm Metab Res 21:445-448, 1989
30. Beller FK, Goebelsmann U, Douglas GW, Johnson AJ: The fibrinolytic system during the menstrual cycle. Am J Obstet Gynecol 23:12-16, 1964
31. Bonnar J, Sheppard BL: Treatment of menorrhagia during menstruation: Randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. BMJ 313:579-582, 1996
32. Ong YL, Hull DR, Mayne EE: Menorrhagia in von Willebrand disease successfully treated with single daily dose tranexamic acid. Haemophilia 4:63-65, 1998
33. Foster PA: The reproductive health of women with von Willebrand disease unresponsive to DDAVP: Results of an international survey. On behalf of the Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the ISTH. Thromb Haemost 74:784-790, 1995
34. Kingman CEC, Kadir RA, Lee CA, Economides DL: The use of levonorgestrel-releasing intrauterine system for treatment of menorrhagia in women with inherited bleeding disorders. Br J Obstet Gynaecol 111:1-4, 2004
35. Andersson K, Rybo G: Levonorgestrel-releasing intrauterine system in the treatment of menorrhagia. Br J Obstet Gynaecol 97:690-694, 1990
36. Lethagen S, Ragnarson TG: Self-treatment with desmopressin intranasal spray in patients with bleeding disorders: Effect on bleeding symptoms and socio-economic factors. Ann Hematol 66:257-260, 1993
37. Leissinger C, Becton D, Cornell C, Gill JC: High-dose DDAVP intranasal spray (Stimate) for the prevention and treatment of bleeding in patients with mild haemophilia A, mild or moderate type 1 von Willebrand disease and symptomatic carriers of haemophilia A. Haemophilia 7:258-266, 2001
38. Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL: DDAVP nasal spray for the treatment of menorrhagia in women with inherited bleeding disorders: A randomised placebo-controlled crossover study. Haemophilia 8:787-793, 2002
39. Rodeghiero F, Castaman G, Mannucci PM: Prospective multicenter study on subcutaneous concentrated desmopressin for home treatment of patients with von Willebrand disease and mild or moderate hemophilia A. Thromb Haemost 76:692-696, 1996
40. Rubin G, Wortman M, Kouides PA: Endometrial ablation for von Willebrand disease-related menorrhagia—Experience with seven cases. Haemophilia 10:477-482, 2004
41. Kadir RA, Economides DL, Sabin CA, Pollard D, Lee CA: Assessment of menstrual blood loss and gynaecological problems in patients with inherited bleeding disorders. Haemophilia 5:40-48, 1999
42. Stirling Y, Woolf L, North WR, Seghatchian MJ, Meade TW: Haemostasis in normal pregnancy. Thromb Haemost 52:176-182, 1984
43. Kadir RA, Lee CA, Sabin CA, Pollard D, Economides Dl: Pregnancy in women with von Willebrand's disease or factor XI deficiency. Br J Obstet Gynaecol 105:314-321, 1998
44. Oravec D, Lichardus B: Management of diabetes insipidus in pregnancy. Br Med J 4:114-115, 1972
45. Rochelson B, Caruso R, Davenport D, Kaelber A: The use of prophylactic desmopressin (DDAVP) in labor to prevent hemorrhage in a patient with Ehlers-Danlos syndrome. N Y State J Med 91:268-269, 1991
46. Chediak JR, Alban GM, Maxey B: von Willebrand's disease and pregnancy: Management during delivery and outcome of offspring. Am J Obstet Gynecol 155:618-624, 1986
47. Mannucci PM: How I treat patients with von Willebrand disease. Blood 97:1915-1919, 2001
48. Ramsahoye BH, Davies SV, Dasani H, Pearson JF: Obstetric management in von Willebrand's disease: A report of 24 pregnancies and a review of the literature. Haemophilia 1:140-144, 1995
49. Greer IA, Lowe GDO, Walker JJ, Forbes CD: Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. Br J Obstet Gynaecol 98:908-918, 1991
50. Beischer NA, Mackay EV: Obstetrics and the Newborn (ed 2). London, UK, Bailliere Tindall, 1986
51. Hanna W, McCarroll D, McDonal T, Painter P, Tuller J, Chen J, et al: Variant von Willebrand's disease and pregnancy. Blood 58:873-879, 1981
52. Khan A, Kadir R, Griffioen A, Pollard D, Shiltagh N, Lee C: A first year clinical review of the multidisciplinary haemophilia/obstetrics and gynaecology clinic at the Royal Free Hospital Haemophilia Centre. Haemophilia 10:144, 2004 (suppl, abstr 28 PO 12)
53. Rodeghiero F, Casterman G, Dini E: Epidemiological investigation of the prevalence of von Willebrand's disease. Blood 69:454-459, 1987