Women with von Willebrand disease

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Keywords
Menorrhagia, delivery, postpartum bleeding

Summary
The clinical presentation of VWD shows sex-related differences of symptoms. In women the most typical symptoms are menorrhagia, bleeding during and after delivery or abortion and bleeding in connection with caesarean section or gynaecological surgery. Menorrhagia is one of the most common symptoms presented to gynaecologists. In 7-20% of menorrhagia the underlying cause is VWD, in our cohort of 185 women with menorrhagia the prevalence of VWD was even 32%. On the other hand in women with VWD menorrhagia with onset at the menarche can be found in 60-93%, influencing substantially their morbidity and quality of life. 

During pregnancy women with mild VWD experience a decrease of bleeding tendency due to an increase of endogenous VWF. But as the VWF concentration drops rapidly after delivery, the post-partum period is often associated with significant bleeding complications. In severe forms of VWD the bleeding risk is high during delivery and postpartum period. Laboratory monitoring and therapeutic measures should be continued for 8-10 days after delivery. During menopause the clinical situation improves for most of the women with mild or moderate VWD.

Menorrhagia

Menstrual problems are typical. Figure 1 shows the type and percentage of menstrual problems in 184 females with VWD including type 1 (94%, severe: 0.54%, moderate: 16.8%, mild: 82%) and type 2 (4.9%) of the haemophilia centre in Frankfurt (47)

Menorrhagia, which means excessive uterine bleedings sometimes with iron deficiency, anaemia and mid-cycle pain, is one of the most common symptoms of women with VWD presenting to gynaecologists. Menorrhagia is defined as a menstrual blood loss of at least 80 ml per month, mostly with a significantly longer duration of menstruation (42). With this definition menorrhagia is difficult to quantify. Measurements based on the pictorial bleeding assessment chart (PBAC) are more practicable and lead to a higher specificity and sensitivity (34). In the majority of cases the cause of bleeding is related to the primary
obstetric and gynaecological pathology and is easily identified (23). But more often than most physicians realise, the bleeding is due to an underlying coagulation defect, predominantly VWD. Several authors identified VWD in 7-20% as cause of menorrhagia: Kadir et al. (19, 22, 23) screened 150 women and found inherited bleeding disorder in 26 patients (17%). The frequency of VWD was 13% (20 patients). Menorrhagia since menarche was noted in 65% of 20 women with VWD (p = 0.001). Dilley et al. (12) screened 121 women with menorrhagia and reported 7% of underlying VWD. Interestingly, a separate analysis by ethnic groups revealed a VWD prevalence of 15.9% among white and for unknown reasons of only 1.4% among black menorrhagia patients (p = 0.01). Bevan et al. (4) found VWD in about 15%, Woo et al. (53) in 13%, Economides et al. (13) in 13%, and Edlund et al. (14) in 20% as the underlying disease (more than 300 patients in total). As Kouides (30) pointed out, that this may only represent the “tip of the iceberg”. Kadir et al. (21) and Kouides et al. (28) could clearly demonstrate morbidity in terms of diminished quality of life (QoL) each month during menstruation in women with menorrhagia. In a second patient cohort of our centre of 185 women with menorrhagia we found a prevalence of VWD of 32% (n = 59) compared to 10% in the general population in our area (31). There were no significant differences between mild and moderate type 1- and type 2 patients. Therefore, testing for bleeding disorders, especially for VWD, should be considered in cases of menorrhagia and no obvious pelvic pathology. In the preceding years several other studies could show that menorrhagia with onset at the menarche can be found in 65-93% of women with VWD. Kadir et Aleldor (23) reported menorrhagia in 65% of women with VWD, Kouides (30) published ca. 80% and Kirtava et al. (25) found 74%. In the study of Ragny et al. (43) menorrhagia was also reported as the most common initial bleeding symptom. The authors investigated 44 women, 38 of them (86%) had VWD type 1. Of the women with menorrhagia 48% had anaemia, 53% took iron replacement and 46% had received transfusions. There was a delay of about 4 years from initial bleeding symptoms at a median age of 12 years to the diagnosis at a median age of 16 years. In our treatment centre VWD was diagnosed even as late as 55 years of age (Fig. 2). This fact demonstrates that VWD still is diagnosed too rare and often very late.

Severe menorrhagia was reported in more than two thirds of type 3 VWD patients. These patients needed transfusions or hysterectomy and were often suffering from iron deficiency (15, 32). In the USA menorrhagia is the most common indication for hysterectomy, accounting for almost half the hysterectomies per year (33). Foster (15) reported in his international survey on the health of women with VWD, that 23% of the woman unresponsive to DDAVP and suffering from menorrhagia underwent hysterectomy to control the bleedings. Hysterectomy in these patients is associated with a high rate of postoperative bleeding.

On the other hand, the relative risk of menorrhagia in women with type 1 VWD is not clear up to now. It might be low as Sadler (49) pointed out, but there also might be a substantial degree of morbidity in these women, as other authors (28) reported. Kadir et al. (22) even reported of 3 hysterectomies in 59 women with type 1 VWD, which were necessary to control menorrhagia. Two studies in Europe and Canada with more than 350 type 1 VWD-patients and more than 1400 controls are ongoing to find the correct prevalence of menorrhagia and bleedings in women with type 1 VWD.
Treatment of menorrhagia

Depending of the type of VWD the treatment of women with menorrhagia includes hormonal therapy, DDAVP (1-desamino-8-D-arginine-vasopressin), tranexamic acid and VWF containing FVIII-concentrates.

Hormonal therapy

The combined oral contraceptive pill (OC) is the most recommended treatment of menorrhagia in patients with VWD. Alperin (1) and later Beller and Ebert (2) and David et al. (10) reported an increase of FVIII-activity and VWF-Ristocetin cofactor activity and also a partial correction of prolonged bleeding time in women with VWD after administration of estrogens. Also the inhibition of endometrial growth, making the mucosa less likely to bleed severely during the time of menstruation might contribute to the mechanism of oral hormonal contraceptives (OCs).

Hormonal therapy comprises oral contraceptives in normal or high dosage, progestational agents (pure or additional), levonorgestrel-releasing intrauterine devices and progestational agents in high dosage. In a multicenter registry (15) of 44 women with type 2 or 3 VWD, which were unresponsive to DDAVP, 77% of the 23 type 3 patients responded well to OCs. On the other hand Koudis et al. (28) reported, that in type 1 patients OCs were ineffective in 76%. These differences between type 1 and type 2/3 patients appear irreconcilable, because the type 2/3 patients have a much lower VWF level than type 1 patients (50).

Siegel and Koudis (50) emphasised that a study with hormonal therapy is needed for all subtypes of VWD and should be done with an objective measure of response such as the pictorial blood chart assessment of menstrual flow (PBAC).

DDAVP

DDAVP or desmopressin is a synthetic analogue of the natural hormone vasopressin. Given in high dosage it releases FVIII, VWF and t-PA from the storage sites in endothelial cells resulting in

- an increase of the corresponding plasma levels,
- an increase of platelet adhesiveness and
- a shortening of the bleeding time (36).

As DDAVP releases the patient’s own FVIII or VWF from the endothelial cells, it only can be effective in mild forms of haemophilia A or VWD (mainly type 1) with a remaining biosynthesis of intact and sufficient factors. In type 2 VWD there is a functional abnormality of the VWF that is mostly not corrected by desmopressin. Therefore, DDAVP seldomly has a sufficient haemostatic effect in type 2 variants and is even sometimes contraindicated in type 2B, because it stimulates the release of the abnormal multimeric VWF, causing platelet aggregation and thus leading to thrombocytopenia (36). In type 2N VWD the levels of FVIII : C increases after desmopressin, but released FVIII circulates only for a relatively short time in the patient’s plasma, because the stabilising effect of VWF on FVIII is impaired by the gene mutation affecting the FVIII binding site of VWF (37). Patients with type 3 VWD usually are unresponsive to desmopressin, because they have neither endogenous VWF-activity nor releasable stores of VWF and usually very low levels of FVIII. Thus, in most type 2 and all type 3 patients VWF-containing FVIII-concentrates are the treatment of choice.

If therapy with DDAVP is indicated, a testdose should be given to ensure that the response is in the intended range and that possible side-effects are acceptable. After a few days of desmopressin the stored VWF and FVIII is released and the clinical effect becomes minimal. If the clinical situation requires further therapy, a switch to VWF-concentrates is indicated. DDAVP can be given intravenously, subcutaneously or as intranasal spray.

For all these reasons DDAVP is a preferred medication for patients with type 1 VWD. The increase of factor concentration is long lasting (8-12 h), so desmopressin also is effective when used prophylactically, for example in women with menorrhagia (46). Preliminary results on the subcutaneous (45) or the intranasal (26) use of DDAVP in menorrhagia have been encouraging, because ca. 80% of the women judged the therapy as effective. But Kadir and coworkers (24) reported the results of a prospective randomised, placebo-controlled cross-over-study with DDAVP nasal spray in 39 women with menorrhagia evaluated with the PBAC and found no significant difference in the PBAC scores of both groups. In another multicenter open-label prospective study (35) intranasal DDAVP was used in 90 patients with VWD type 1 for the treatment of menorrhagia. The response was rated as good or excellent in 92% of treatments.

Our experience with intranasal DDAVP, especially in home treatment, is very good and we recommend two intranasal sprays (150 µg) one in each nostril (300 µg/d) for 3 days. Side effects might be water retention, oedema and hyponatraemia. Given subcutaneously, the dose of DDAVP should be 0.3 µg/kg body weight once daily for 3 consecutive days. Further studies with DDAVP to evaluate the optimal treatment routes and optimal dosing in patients with different types of VWD are needed.

Tranexamic acid

Other treatment alternatives for menorrhagia in women with VWD are inhibitors of fibrinolysis, especially tranexamic acid, given at a dose of 10-12 mg/kg body weight orally 3 times a day from the start to the end of the menstrual bleeding. It has been shown that endometrial fibrinolytic activity is markedly increased just before the menstrual period and that women suffering from menorrhagia have significant higher activity (48). Antifibrinolytics reduce the fibrinolytic activity to normal levels by inhibiting the activation of plasminogen to plasmin and thereby stabilise preformed clots and prolong their dissolution (41). Bonnar and Sheppard (5) published a significant reduction of menstrual blood loss of 54% in women with menorrhagia after intake of tranexamic acid. Similar effects were observed by Ong et al. (41) in 3 patients with VWD type 2 and one patient with VWD type 1 even after a single daily dose treatment with tranexamic acid.

The therapy with anti-fibrinolytics has the advantage that they have an effect also
in more severe forms of VWD and that the use of hormones and factor-concentrates can be reduced. Side effects might be nausea or occasional gastrointestinal symptoms such as vomiting and diarrhoea. An increased risk of thrombosis, which initially was discussed, could not be confirmed (3).

**FVIII**

If hormonal therapy, therapy with DDAVP and with anti-fibrinolytics fail to reduce menorrhagia in women with VWD to an acceptable level, the substitution of a virus-inactivated VWF-containing FVIII-concentrate has to be considered. There are several VWF-containing FVIII-products on the market, but only a few of them have acceptable von Willebrand activities and even less are licensed for therapeutic use of VWD (for example Haematr HS, Aventis Behring). It could be shown that the specific VWF-activities of the concentrates depend largely on their content of high molecular weight VWF-multimers (HMWM) (52).

Concentrates with a high concentration of HMWM are most suitable and should be preferred. Several clinical studies demonstrate good clinical effectiveness of these concentrates in prophylaxis and therapy of bleeding in VWD-patients. The dosage to reduce bleeding to normal blood loss depends on the individual situation of the patient and should be adapted by the treating physician. In average a daily dose of 20-40 I.U. FVIII/kg body weight during the menstrual period can be recommended.

**Surgery**

The last options to control menorrhagia are surgical or radiological interventions like hysterectomy, endometrial ablation or electro-coagulation. These options should only be taken into consideration in those rare cases, where all the other mentioned therapies were not capable to control the bleedings. But reviewing the literature leads to the impression that especially hysterectomy is performed much too often without clear indication.

These surgical interventions are associated with a high rate of postoperative bleeding complications and of course lead to sterility. For that reasons surgical interventions are options mainly for women in the postchildbearing phase.

**Pregnancy**

During pregnancy most of the women with mild VWD have only little disease-related problems and report a decrease of bleeding tendency (20). Their FVIII- and VWF-levels increase significantly, beginning at the end of the first trimester, and very often become normal before delivery. In the literature, this effect sometimes is called the gestational palliation (27). This effect is less pronounced in type 2 VWD, where the abnormal multimeric structure of VWF remains unchanged, and it is absent in type 3. No considerable rise of the FVIII-level can be expected in type 2N VWD-patients, because the FVIII binding capacity of the altered VWF does not improve during pregnancy (11, 40). As the bleeding tendency of patients with type 2 and 3 VWD is not or only very little reduced during pregnancy, laboratory monitoring and factor substitution if necessary are recommended. Some patients with type 2B VWD develop thrombocytopenia in the third trimester of pregnancy, which most likely is due to the increased synthesis of abnormal VWF-multimers. This abnormal VWF spontaneously binds circulating platelets, followed by platelet aggregation and a drop in platelet count, which normally shows its lowest value 1-3 days before delivery. A few days later, immediately after delivery, the tendency suddenly reverses and the platelet count increases again. Casonato et al. (8) could demonstrate, that the VWF multimeric pattern shows a strict but inverse correlation with the platelet count.

Treatment with IgG and prednisolone could not improve the platelet situation (18). In the case of very low platelet counts it seems to be obvious to transfuse platelets. Giles et al. (16) could show that the substitution of platelets might not be necessary, if the patients are monitored very closely. Several authors (17, 18, 51) reported that treatment with VWF-containing FVIII-concentrates can cause a resolution of thrombocytopenia and later on enable a successful management of delivery.

**Miscarriage, abortion**

Different estimations according to the literature concern the incidences of miscarriage and abortion in pregnant women with VWD. Foster (15) reported an incidence of miscarriage of 22%, which is much higher than normal, but he also mentioned that they appeared clustered, because 10 of the 15 miscarriages occurred in just four of the women. Kadir et al. (22) noted miscarriages in 33% of 115 females with VWD: 21% of the patients had recurrent abortions.

Other authors like Mannucci (37) came to the conclusion that miscarriages in women with VWD are no more frequent than in the normal population. It is unclear, whether this difference is due to the limited data on this problem or reflects the progress in modern management of VWD. In case of early abortion – induced or spontaneous – up to the beginning of the second trimester there is a considerable risk of copious bleeding, because at that time the FVIII- and VWF-activities are still low. But the patients respond well to desmopressin or VWF-concentrates and a therapy with VWF-concentrate or in case of induced abortion a prophylaxis with desmopressin or VWF-concentrate can avoid major bleedings.

**Labour, delivery, postpartum period**

Labour, delivery and postpartum period are often associated with significant bleeding complications. The bleeding risk depends on the type of VWD and the FVIII and VWF levels reached at the time of delivery. Women with type 2 and type 3 VWD usually have low levels even at the end of pregnancy and therefore need prophylactic therapy already in the first stage of labour. But even women with mild VWD and postpartum normal levels of FVIII and VWF have a substantial risk of postpartal bleed-
ing, because the factor levels fall rapidly after delivery to the level prior to the pregnancy. Up to 25% of affected pregnant women experience postpartum haemorrhage. The incidence of primary postpartum haemorrhage (<24 h) was 18.5% in the cohort of Kadir et al. (19). 20% of the patients reported secondary postpartum haemorrhage (>24 h), even 1 week after delivery. Kouides (29) stated that in very severe cases the care giver must be aware that haemorrhage can even occur up to 5 weeks postpartum.

In another study the risk of primary postpartum haemorrhage even was as high as 37.5% in patients with type 2 VWD who did not receive prophylactic FVIII-treatment (44). The risk of postpartum bleeding complications cannot be predicted with certainty, neither by past history of bleeding episodes nor by haematological laboratory tests. Many authors think that the FVIII : C level during delivery and postpartum period might be the best predictor for the bleeding risk.

Their experience is that the risk for bleeding is minimal when FVIII : C levels are higher than 40 U/dl and can be significant when they are lower than 20 U/dl (37). The severity of bleeding varies not only among different patients but also between different pregnancies of the same woman. Women may experience a serious postpartum haemorrhage with one pregnancy and have no complications with the next one.

For that reasons the management of delivery should start 1-2 days before parturition with monitoring the coagulation parameters. A normal delivery can be expected in women with mild VWD and FVIII/VWF levels above 50%, a prophylactic therapy for spontaneous delivery seems not to be necessary. In case that the FVIII and VWF activities are not satisfying, what generally is the case in type 2 and type 3 VWD-patients, prophylactic treatment should be initiated.

Treatment modalities during labour comprise DDAVP in type 1, VWF-containing FVIII concentrates in type 2 and type 3, avoidance of vacuum or forceps delivery and caesarean section in prolonged or complicated labour. Replacement therapy with VWF concentrates will be required to cover delivery or caesarean section in patients with type 3 VWD. The gynaecologist should care for good surgical haemostasis and effective uterine contraction, because that usually compensates for a prolonged bleeding time (9). In patients with type 1 or type 2 VWD vaginal delivery is usually safe and can be recommended. Vaginal delivery is also considered safe in patients with type 3 VVS, if they receive sufficient prophylactic substitution of VWF (7).

To avoid postpartal bleeding after the decrease of the factor levels, the laboratory monitoring should be continued for the following 8-10 days. Treatment with DDAVP or VWF concentrates may be required for the first 8 days postpartum. The dosing of factor concentrate has to be tailored to the individual situation. Despite all these problems, women with VWD should nevertheless not be discouraged to become pregnant, as long as their pregnancies are observed also by a haematologist experienced in coagulation disorders.

Menopause

After half of her life the woman’s hormonal situation changes and the menopause begins. As a positive effect for women with mild and moderate VWD, the values of FVIII and VWF increase during the first years, this time for ever. The disease related symptoms improve with age and may become minor or even disappear by the fifth or sixth decade. The need for therapy will reduce accordingly.

Conclusion

The von Willebrand disease has a major impact on morbidity and quality of life for affected women. Depending on the severity of the disease and on the individual bleeding tendency, they need occasionally or regularly medical treatment of menorrhagia and face critical situations during pregnancy and delivery of their children. 50 years ago the mortality of patients with VWD was very high.

Actually, we have very good treatment options for all types of VWD and for all bleeding situations. Quality of life could improve dramatically, if the patients would get access to these therapies. Unfortunately, the knowledge of modern von Willebrand therapy did not yet reach all the physicians and it seems to be obvious that many of the women, especially those with mild or moderate VWD, are not treated optimally. There are lots of reports documenting for example that only a few percent of physicians would consider VWD as cause of menorrhagia in women of reproductive age or showing that VWD is diagnosed only in a few percent of patients suffering from preventable bleeding complications during surgeries. It will be the challenge for the next years to spread the knowledge of modern therapy options and to intensify the cooperation between haematologists and other physicians, for example gynaecologists. The evaluation and treatment of menorrhagia and the management of pregnancy and delivery of women with VWD may be very complex and should no longer be exclusively the task of the gynaecologist, but much more the task of interdisciplinary teams, as we have already in the comprehensive haemophilia care centers (CCC). Comprehensive care of women with VWD should result in reduction of unnecessary surgical interventions for menorrhagia (like hysterectomy), in improvement of quality of life during menses, which is reduced in 40% of these women (47) and should result in optimising peripartal management.

Comprehensive care teams should also be capable to discuss and prepare consensus guidelines on the management of women with von Willebrand disease.

References

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