

# Menorrhagia and bleeding disorders in adolescent females

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## Keywords

Menorrhagia, adolescents, bleeding disorders, endometriosis, miscarriage, von Willebrand's disease

## Summary

In women, von Willebrand disease (VWD) is the most common inherited bleeding disorder. Since VWD and other inherited bleeding disorders are autosomal disorders, they affect women and men. Menorrhagia, or heavy menstrual bleeding (HMB), is the most common symptom of women with bleeding disorder experience. Objectively, it is defined as bleeding that lasts for more than seven days or results in the loss of more than 80 ml of blood per menstrual cycle. The prevalence of menorrhagia in a woman with a bleeding disorder ranges from 32 to 100% in patients with VWD, from 5 to 98% in patients with a platelet dysfunction and from 35 to 70% in women with a rare factor deficiency. A detailed history and a careful physical exam are the first steps towards a diagnosis in adolescents, adding a PBAC > 100 increased the sensitivity of the screening tool further to 95%. Laboratory testing should be made at the time of menstrual bleeding in an effort to capture the lowest level of VWF:Ag and FVIII:C. **Treatment options** for menorrhagia in VWD: (1) antifibrinolytic therapy with tranexamic acid, (2) the non-transfusional agent desmopressin (DDAVP), (3) purified blood products that contain factor VIII and VWF concentrated from plasma and (4) hormonal preparations.

## Schlüsselwörter

Hypermenorrhoe, Jugendliche, Gerinnungsstörung, Endometriose, Fehlgeburt, von Willebrand-Syndrom

## Zusammenfassung

Das von-Willebrand-Syndrom (VWS) ist die häufigste angeborene Blutgerinnungsstörung. Pathologisch verstärkte bzw. verlängerte Monatsblutungen (so genannte Menorrhagie) gehören zu den häufigsten Symptomen bei Frauen mit Gerinnungsstörungen. Objektiv gesehen sind diese starken Monatsblutungen so definiert, das der Menstruationszyklus mehr als sieben Tage andauert oder aber der Blutverlust mehr als 80 ml pro Zyklus beträgt. Die Prävalenz der Menorrhagie bei Frauen mit einer Blutgerinnungsstörung reicht von 32 bis 100% bei Patientinnen mit VWS, 5 bis 98% bei Patientinnen mit einer Thrombozytenfunktionsstörung und 35 bis 70% bei Frauen mit seltenen Faktorenmangelzuständen. Eine detaillierte Anamnese und eine sorgfältige körperliche Untersuchung sind die ersten Schritte zur Abklärung einer Menorrhagie, bei Vorliegen eines PBAC-Scores > 100 erhöht sich die Empfindlichkeit des Screening-Tools weiter auf 95%. Labortests sollten zum Zeitpunkt des 2.–3. Tages der Monatsblutung durchgeführt werden, in dem Bemühen, den untersten Normwert der von-Willebrand-assoziierten Laborwerte erfassen zu können. **Behandlungsoptionen** für Menorrhagie bei einem VWS: (1) antifibrinolytische Therapie mit Tranexamsäure, (2) Desmopressin (DDAVP), (3) virusinaktivierte Plasmafaktoren, die Faktor VIII und VWF enthalten und (4) Hormonpräparate.

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## Menorrhagia und Blutungsstörungen bei adolescenten Frauen

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## Gynaecological manifestation of bleeding disorders

### Menorrhagia

In women, von Willebrand disease (VWD) is the most common inherited bleeding disorder. VWD and other inherited bleeding disorders are autosomal disorders and equally likely affect women and men. Initially, VWD was called pseudohaemophilia; in this study women were affected.

### The index case

A girl at the age of eight years described multiple bleeding symptoms (easy bruising, epistaxis) and ultimately exsanguinated to death during her fourth menstrual cycle at age of 13 (1).

Menorrhagia, or heavy menstrual bleeding (HMB), is the most common symptom that women with bleeding disorders experience.

HMB is defined as bleeding that lasts for more than seven days or results in the loss of more than 80 ml of blood per menstrual cycle (2).

The average menstrual blood loss is 25–80 ml without significant clots. This definition is taken from population studies, which have shown that approximately 10% of women experience losses of over 80 ml per cycle (3).

Attempts to measure the quantity of menstrual blood loss can be difficult in clinical practice. One study found that variables that predicted a blood loss higher than 80 ml per menses were clots greater than one inch, low ferritin levels, or changing a pad or tampon more than hourly (flooding) (4). A prospective method of quantifying menstrual blood loss includes

the use of a pictorial bleeding assessment calendar (PBAC) (► Fig. 1).

The PBAC score has been validated in adult women with more than 80% sensitivity and specificity for scores higher than

100. The total menstrual score of more than 100 was associated with a blood loss of more than 80 ml (5). Subjectively, menorrhagia is defined as a complaint of excessive regular menstrual bleeding

occurring over several consecutive cycles in women during their reproductive years.

## Prevalence of VWD

The prevalence of menorrhagia in a woman with a bleeding disorder ranges from

- 32 to 100% in patients with VWD (6),
- 5 to 98% in patients with platelet dysfunction (7–8) and
- 35 to 70% in women with a rare coagulation factor deficiency (9–12).

The prevalence of the laboratory diagnosis of VWD in the general population is estimated to be approximately 1% (13).







Studies evaluating the prevalence of VWD in adolescents with menorrhagia included more than 540 patients (► Tab. 1) with a prevalence between 3% and 36%, depending on the clinical setting (12, 14–22).

## Haemorrhagic ovarian cysts

Haemorrhagic ovarian cysts are less common, but perhaps a more specific manifestation of a bleeding disorder. Women who have VWD or another bleeding disorder can have ovulation-associated bleeding that results in haemorrhagic ovarian cyst formation and bleeding into the peritoneum, broad ligament, or retro peritoneum. While these cysts were not necessarily haemorrhagic ovarian cysts, an increased incidence of haemorrhagic ovarian cysts may have contributed to the higher prevalence of cysts reported in women with VWD (23–25).

## Endometriosis

Endometriosis has been noted in women with bleeding disorders. Although there is disagreement as to the etiology of endometriosis, the prevailing theory is that it results from retrograde menstruation (26). Retrograde menstruation is the reflux of menstrual blood out of the uterine cavity (27). Women with endometriosis have been shown to suffer from heavier menstrual

NAME:		SCORE:							
DAY START:		DAY							
TOWEL	1	2	3	4	5	6	7	8	
									
									
									
CLOTS/ FLOODING									
TAMPON	1	2	3	4	5	6	7	8	
									
									
									
CLOTS/ FLOODING									
<b>scores</b>	<ul style="list-style-type: none"> <li>• A lightly stained towel will score 1 point,</li> <li>• a moderately stained towel 5 points.</li> <li>• A towel which is saturated with blood will score 20 points.</li> <li>• A lightly stained tampon will score 1 point,</li> <li>• a moderately stained tampon 5 points.</li> <li>• A tampon that is fully saturated will score 10 point.</li> <li>• A clot the size of               <ul style="list-style-type: none"> <li>– 1p scores 1 point,</li> <li>– a 50p sized clot scores 5 points and</li> <li>– flooding also scores 5 points.</li> </ul> </li> </ul>								
<b>results</b>	Once you have finished your period total up your scores. A score of 100 or greater may indicate that you have heavy periods and you should seek advice from your doctor. However if your score is less than 100 and you have concerns about your period you should always consult your GP.								

**Fig. 1** Pictorial blood assessment chart and scoring system for assessment of menstrual blood loss (reproduced with kind permission by John Wiley and Sons from: Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990; 97: 734–739)

bleeding (28). Because their menses are heavier, women with bleeding disorders may be more likely to experience retrograde menstruation and, consequently, endometriosis.

## Miscarriages

There are several case reports and series documenting the increased risk of miscarriage resulting in fetal loss or premature delivery among women with deficiency of factor XIII (29) or fibrinogen (30). Reports of miscarriage in women with bleeding disorders are summarized in ► Table 2.

## Screening for bleeding disorders

### Patient's history

A detailed history and a thorough physical exam are the first steps towards a diagnosis in adolescents with bleeding disorders. Bleeding history red flags warranting screening is summarized in the ► box.

In a recent study by Phillip, a screening questionnaire of eight questions (questions based on the historical red flags) resulted in 82% sensitivity for detecting any bleeding disorders (VWD, platelet function defect, or clotting factor deficiency). Adding a PBAC > 100 increased the sensitivity of the screening tool to 95% (36).

### Laboratory testing

An ideal screening panel to rule out any bleeding disorder in an adolescent presenting with menorrhagia is not yet clearly defined.

Laboratory testing should include a complete blood count to assess the haemoglobin level and to exclude thrombocytopenia. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) should be part of an initial screen although not sensitive for bleeding disorders. Other tests to investigate qualitative (thrombin clotting time) and quantitative (clottable fibrinogen) defects of fibrinogen are helpful. Testing for VWD includes

**Tab. 1** Prevalence studies in bleeding disorders associated with menorrhagia in adolescents

study (ref.)	n	setting	VWD (%)
Chi et al. 2010 (22)	42	haemophilia treatment centre	20
Mikhail et al. 2007 (19)	61	outpatient haematology clinic	36
Jaysainghe et al. 2005 (17)	106	inpatient and outpatient	5
Philipp et al. 2004 (12)	25	outpatient primary care clinic	4
Kanbur et al. 2004 (18)	47	inpatient	4
Bevan et al. 2001(14)	71	emergency department, urgent care and inpatient	3
Oral et al. 2001 (20)	25	inpatient	8
Smith et al. 2001 (21)	46		5
Falcone et al. 1994 (16)	61		0
Claessens et al. 1981 (15)	59		8

**Tab. 2** Miscarriages in women with bleeding disorders

study (ref.)	sample size, population	type of study	prevalence of problem
Chediak et al. 1986 (31)	10 pregnancies in 6 women with VWD	case series	3/10 (30%)
Foster 1995 (32)	69 pregnancies among 31 women with VWD		22%
Kadir et al. 1998 (33)	84 pregnancies in 31 women with VWD		18/72 intended pregnancies (25%)
Kirtava et al. 2003 (34)	86 women with VWD and 70 controls with at least one pregnancy	case control study	15% of pregnancies among cases 9% among controls (p = 0.05)
Kadir et al. 1997 (35)	82 pregnancies in 32 haemophilia carriers (24 with a 8 with B)	case series	22/72 intended pregnancies (31%)
Lak et al. 1999 (30)	18 women with afibrinogenaemia		3/18 (17%) with > consecutive miscarriages
Burrowas et al. 2000 (29)	16 women with factor XIII deficiency	summary of case reports	10/16 (63%) with recurrent miscarriages

- ristocetin cofactor activity (VWF:RCo),
- factor VIII activity (FVIII:C), and
- VWF antigen level (VWF:Ag).

There is a high degree of variability in VWF assays over time as well as with routine stressors such as blood drawn. Therefore, it is recommended to test more than once for a definitive diagnosis. It is also suggested that at least one of these testing should take place at the time of menstrual bleeding in an effort to capture the lowest level of VWF:Ag and FVIII:C (37, 38).

## Treatment of adolescents with VWD

Treatment of VWD is often complex because a combination of therapies is often required (39). Furthermore, VWD subtypes subtypes respond differently to treatment (40). Therefore, a haematologist should manage adolescents with menorrhagia caused by bleeding disorders with expertise in treating VWD. There are four main agents used to stop and/or pre-

## Screening

### Bleeding history red flags

1. Prolonged bleeding from trivial wounds lasting more than 15 minutes, or recurring spontaneously within seven days.
2. Heavy, prolonged, or recurrent bleeding after surgical procedures, such as tonsillectomy.
3. Bruising with minimal or no apparent trauma with a lump under the bruise.
4. Spontaneous nose bleeds lasting more than 10 minutes or needing medical attention.
5. Heavy prolonged, or recurrent bleeding after dental extractions.
6. Blood in the stool unexplained by anatomic lesions such as stomach ulcers or colonic polyps.
7. Anaemia requiring treatment or blood transfusion.
8. Heavy menses characterized by clots greater than an inch in diameter and/or changing a pad or tampon more than hourly, or resulting in anaemia and/or low iron stores.
9. Blood relative with a bleeding disorders such as von Willebrand disease or haemophilia.

vent excessive bleeding for VWD-related menorrhagia (41):

### Antifibrinolytic therapy

Antifibrinolytic therapy is performed with either

- tranexamic acid (Cyclokapron®) or
- ε-aminocaproic acid (Amicar®).

Tranexamic acid, an antifibrinolytic agent, has been shown to significantly (40–50%) reduce menstrual blood loss in women with HMB (42). However, it does not reduce the duration of menses or regulate the menstrual cycle. Aminocaproic acid has also been successfully used to decrease uterine bleeding, but it is less potent and has more side effects than tranexamic acid.

Tranexamic acid had been used for many years in Europe and elsewhere, but

had not been approved for use in the United States until recently (November 2009) for fear of thromboembolic complications. A recent case control study on thromboembolic disease and tranexamic acid found an odds ratio 3.2 for the use of tranexamic acid in cases (thromboembolism) versus controls (no thromboembolisms), but this value did not reach statistical significance (CI 0.65–15.78) (43).

The most side effect is gastrointestinal symptoms (nausea and diarrhea). These are the main reason for discontinuing treatment or reducing the dose resulting in reduced efficacy. Tranexamic acid has successfully been used for the control of menorrhagia in women with a variety of known bleeding disorders (22, 44).

### Desmopressin

The non-transfusional agent desmopressin (DDAVP, 1-desamino-8-D-arginine vasopressin) is a synthetic analogue of the antidiuretic hormone vasopressin (45–47). It increases plasma concentration of VWF and factor VIII in the circulation and increases platelet adhesiveness.

DDAVP is commonly used for prevention and treatment of bleeding episodes in some patients with mild bleeding disorders, mainly type 1 VWD and haemophilia A. For home treatment in women with bleeding disorders and HMB, DDAVP as intranasal spray has been shown to be effective with a significant reduction in quality of life (48). In the same study, however, tranexamic acid was shown to be more effective. Concomitant use of DDAVP intranasal spray and oral tranexamic acid has been shown to be more effective in reducing menstrual blood loss (49) compared to DDAVP alone. In addition, this regime also helps reduce the necessary dose and duration of DDAVP use, thus reducing the potential risk of hypernatraemia. Hypernatraemia and potentially water intoxication is a small risk of DDAVP use, due to its antidiuretic effect.

Common side effects of DDAVP are mild tachycardia, headache, and flushing. Tranexamic acid alone or in combination of DDAVP provides a good option for

treatment of HMB in adolescent girls, especially very young girls and those who do not accept hormonal treatments. These agents can also be used in combination with hormonal therapies during the period or breakthrough bleeding.

### Factor VIII and VWF concentrates

In adolescents with severe bleeding disorders, regular prophylaxis with specific clotting factors may be necessary to control HMB not responding to other medical treatments. Purified blood products that contain factor VIII and VWF concentrated from plasma (50) can be administered during menstruation or throughout the menstrual cycle for those with prolonged irregular bleeding or recurrent ovulation bleedings.

### Hormonal preparations

Combined contraceptive hormones, containing both estrogen and a progesterone, reduce menstrual loss by inducing regular shedding of a thinner endometrium. Combined hormonal contraceptives are administered as combined

- oral contraceptives (COC),
- transdermal patches and
- vaginal rings.

COC is the method of choice in adolescents. COCs are useful for cycle regulation and improved menstrual pain and premenstrual tension. They are also highly reliable and safe contraceptives for these girls with no adverse effects on their future fertility or attainment of their peak bone mass (51). COC is commonly used to control abnormal uterine bleeding (AUB) in girls and women with bleeding disorders, with an added advantage of preventing ovulation bleeding.

The most serious side effect is venous thromboembolism. However adolescent girls in general and those with bleeding disorders in particular have a very low inherited risk of thrombosis. Minor side effects are usually temporary and induced headache, nausea and vomiting, breast tenderness, fluid retention, and skin changes.

The levonorgestrel containing intra-uterine system (LNG-IUS, Mirena) reduces menstrual loss by suppressing endometrial growth with continuous release of levonorgestrel 20 µg/24 hours. LNG-IUS is regarded as the most effective medical treatment for HMB and a highly efficient contraceptive. Its efficacy has been shown for managing HMB in women with bleeding disorders (52, 53). However, it is not often considered in adolescents due to lack of data on its acceptability and safety in these patients. Among 179 adolescents (aged 11–19 years) in New Zealand, a year continuation rate for LNG-IUS was 85% and cumulative incidence of expulsion was 8%, which are both comparable to the rates reported of adult female population (54).

In a study of 42 adolescent girls, regular prophylaxis was required for four girls with severe bleeding to control abnormal uterine bleeding in addition to the use of tranexamic acid and combined hormonal contraception (22).

Non-steroidal anti-inflammatory drugs such as ibuprofen, naproxen among others, have been shown to decrease menstrual blood loss in adult patients with menorrhagia (55).

## Conclusion

A multidisciplinary assessment approach by haematologists and gynecologists is crucial in the management of girls with bleeding disorders.

## Conflicts of interest

The author declares, that she has no conflict of interest regarding the subject of research reported in the manuscript.

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