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ORIGINAL ARTICLE

Women with bleeding disorders

Managing women-specific bleeding in inherited bleeding disorders: A multidisciplinary approach

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Abstract

Introduction: Multidisciplinary management of women-specific bleeding is important to preserve quality of life, healthy reproduction and social participation of women and girls with bleeding disorders (WBD).

Aim: To support appropriate multidisciplinary care for WBD in haemophilia treatment centres.

Methods: Two case examples are presented and management issues discussed from different health care perspectives, including the nurse, patient, psychologist, gynaecologist, geneticist, psychosexual therapist and haematologist.

Results: Woman with bleeding disorders may experience heavy menstruation from menarche onwards. This has a physical and psychosocial impact requiring a multidisciplinary approach. If a woman with an inherited bleeding disorder desires to become pregnant, preconception counselling is essential, to discuss genetic diagnosis, state of the art treatment options for the bleeding disorder in question and possible choices to prevent having an affected child, as well as maternal bleeding risks during conception, delivery and the post-partum period.

Conclusion: Adequate management and good education of WBD requires a patient-centred multidisciplinary approach with experienced specialists in a haemophilia treatment centre.

KEYWORDS
bleeding disorder, haemophilia, heavy menstrual bleeding, post-partum haemorrhage and reproduction, von willebrand disease, women

1 | INTRODUCTION

Women and Girls Bleeding Disorders (WBD) face specific challenges associated with reproduction and the menstrual cycle. Multidisciplinary management is important to preserve quality of life and social participation.[1] Here, we present two case examples to discuss the management of WBD from different perspectives of involved healthcare professionals, including the aspect of sexuality, and the patients' perspective. Our aim is to support appropriate multidisciplinary care for WBD in haemophilia treatment centres (HTC).

2 | CASE 1

An 11-year-old girl with severe type 2A von Willebrand disease (VWD), with von Willebrand Factor (VWF) antigen 40 IU/dl, VWF activity 5 IU/dl and factor VIII 53 IU/dl consults her paediatric haematologist. Her medical history includes an uncomplicated adenotonsillectomy at the age of 4 years covered with VWF concentrate. Recurrent epistaxis has been controlled with cauterization once and occasional use of Desmopressin and Tranexamic acid. She is an active girl who participates in sports (swimming), about to go to secondary school and to have her first menstruation.

2.1 | Question for the multidisciplinary team

Over 80% of women with VWD experience heavy menstrual bleeding[2,3]: how should this girl and her family be prepared for the menarche?

2.1.1 | Nurse perspective

Haemophilia treatment centres nurses have an important role in HTC multidisciplinary team providing education, being accessible for patient's questions and uncertainties/worries and making sure that the right team members are contacted in case of a specific problem of concern. In educating, it should be taken into mind to talk with both parents and the girl in 'understandable' language (no jargon) and to adjust the mode of education to the patient's age and culture. Education of WBD should include information on the normal menstrual cycle and on symptoms of iron deficiency. Next to information on pads and tampons, information about use of menstrual cups—how to measure blood loss and if 'period poverty' is an issue, the need for (psycho)social support can be explored in their families. The Pictorial Blood Loss Assessment Chart (PBAC) can be used to measure (ab)normal menstruation; a PBAC score >100 corresponds to abnormal blood loss.[4] Families can be made aware of mobile applications (apps) that track periods and blood loss, for example www.sisterhoodapp.com, if appropriate in the local setting. Also other practical issues should be discussed, such as information about sports participation and the need to have pads available at school. Basic sexual education, including information on how to manage bleedings, should also be part of the conversation. Adolescent girls should be prepared for transition to adult care, for example starting with an appointment by an adult nurse at age 14–15 years.

In case of heavy menstrual bleeding (HMB), the girl should have medication available to treat her coagulation defect (such as Tranexamic acid, Desmopressin and/or clotting factor concentrate). If severe menstrual pain occurs they should know what kinds of painkillers are allowed; non-steroidal anti-inflammatory drugs (NSAIDs) preferably not to avoid additional platelet dysfunction, cyclo-oxygenase-2 (COX-2) selective NSAIDs are allowed since these drugs comprise platelet function to a lesser extent. The aim of hormonal treatment should be explained mainly as a treatment of HMB rather than as an contraconceptive although both effects should be discussed. Haemoglobin and ferritin levels should be checked regularly in case of HMB.

Women and Girls Bleeding Disorders suffering from HMB are likely to experience psychosocial issues which can affect academic and social pursuits.[5] Offering peer support can help to maintain their self-esteem, as well as extending management beyond the hospital, teaching and organizing home treatment for those who require regular factor replacement therapy and liaising with school or place of work when required. If bleeding problems interfere with social participation, a social worker should be involved.

2.1.2 | Psychologist perspective

Based on the clinical experiences, menarche may be a traumatic experience affecting quality of life and even provoke a post-traumatic stress syndrome (PTSS). HMB has negative impact on the quality of life in WBD, impairing their daily activities and social life.[6,7] The health-related quality of life (HRQoL) in 13 years old girls with a bleeding disorder is lower compared to their healthy peers.[8] In contrast, there is no apparent difference in psychosocial functioning and HRQoL between young adult women with a bleeding disorder compared to peers.[9] However, women with bleeding disorders participating in a large survey stated that they had mainly problems on reproduction and sexual relations. They also felt more fatigued.[10] Psychosocial support is important to prevent further deterioration which may hamper the social development of these girls.

To check whether reference to a psychologist is indicated, standard screening with patient-reported outcome measurement instruments, such as HRQoL questionnaires, can be performed ahead of an outpatient clinical visit. Ideally, a psychologist, or at least a social worker, is part of the multidisciplinary team to discuss WBD who experience serious psychosocial issues. In case of PTSS eye movement desensitization reprocessing treatment by a psychologist is indicated.[11] When problems like fatigue, acceptance, shame or fear interfere with normal social functioning, treatment with cognitive behaviour therapy may be indicated.

2.1.3 | Gynaecologist perspective

Menstrual disorders are common in adolescent girls. Menstrual periods can be heavy and irregular, usually secondary to anovulatory cycles caused by immaturity of the hypothalamic-pituitary-ovarian axis. Adolescent girls with inherited bleeding disorders are at a higher risk of HMB; often starting from menarche with a significant health implications such as anaemia, hospitalization and need for transfusion of blood or blood products. HMB has a negative impact on quality of life, can be a source of distress for adolescent girls and may affect their school attendance and performance as well as their social life.[12]

In case of suspected heavy menstrual bleeding (HMB), assessment of menstrual blood loss using the PBAC score is useful. Alternatively, narrative assessment should be adopted; excessive bleeding is defined as prolonged (>7 days), and/or the need to change a pad every 2 h or more.[13] Careful history taking is important. Pelvic examination and ultrasound, if appropriate, may reveal an additional reason for HMB. The goals of HMB treatment are to reduce morbidity, prevent iron deficiency and improve quality of life through reducing menstrual blood loss and attainment of a predictable pattern of menstruation.[14]

Treatment options for HMB depend on age, menstrual pattern, the need for contraception and patients tolerability and acceptability of available treatment options. Management of HMB in adolescents is usually medical and there are several haemostatic and hormonal options that can be used singly or in combination (Table 1). However, there are specific considerations when using these agents in adolescent girls that must be incorporated into multidisciplinary and shared decision-making with the girls and their family. This is ideally provided in a joint clinic, where the experts can agree on optimal use of various treatments and assess the girls in one visit. WBD

TABLE 1 Haemostatic and hormonal treatment options for WBD with HMB

	Side effects	Efficacy
Haemostatic therapies		
Tranexamic acid, 1 g 3–4 times a day	Gastro-intestinal side effects, mainly nausea and diarrhoea	Significantly reduces menstrual loss but does not reduce the duration of the menses nor does it regulate the menstrual cycle
Desmopressin as a nasal spray or subcutaneous injection	Palpitations, headache and facial flushing. Water retention and hypernatremia if fluid restriction rules are not adhered after administration	Effective in specific bleeding disorders (carriers of haemophilia A, type 1 VWD and some of type 2 VWD and some platelet function defects)
Clotting factor concentrates	Rarely inhibitor development	Used effectively in HMB in VWD.
Hormonal therapies		
Combined hormonal contraceptive (oral, or patch or as a vaginal ring)	Breakthrough bleeds Headache, nausea, fluid retention and breast tenderness, hypertension, leg cramps and skin changes	Reduce menstrual loss, the duration of the menses and regulates the menstrual cycle; reduce the number of menstrual cycles when given continuously or extended (two months or more). Prevents ovulation bleeding and improves menstrual pain
Levonorgestrel releasing IUD	Irregular spotting after insertion, hormonal side effects (weight gain, bloating, breast tenderness, acne, nausea, and mood changes). Insertion in adolescents, especially those not sexually active is difficult and under general anaesthesia can be considered.[12] Ovulation bleedings can still occur[a]	Suppress endometrial growth, reduce menstrual blood loss, and increase in haemoglobin levels, in 60% of cases amenorrhoea after 12 months of use.[33]
Cyclical progestogens orally in a cycle of 21 days	Due their side effects (weight gain, breast tenderness and depression) compliance with treatment is low	When used for 21 days per cycle (Day 5–26) reduces menstrual blood loss
Progesterone only contraceptives orally as a progesterone only pill or as subcutaneous progestogens, like etonogestrel (Implanon®) or as a intramuscular or subcutaneous injection of depot medroxyprogesterone acetate	Breakthrough bleedings are common as well as mood disturbances	Reduce menstrual blood loss by inducing amenorrhoea

Abbreviations: HMB, heavy menstrual bleeding; IUD, intra-uterine device; VWD, von Willebrand disease.

[a]IUDs containing levonorgestrel do not suppress ovulation, so ovulation bleeding can still be a problem. In such cases, the use of hormonal IUD can be combined with a combined oral contraceptive pill.[32]

value provision of care in such models with a high level of satisfaction and better compliance to treatment.[15]

2.1.4 | Patients' perspective

A 42-year-old woman, suffering from severe VWD, shared her personal experience with the menarche. This was very traumatic. She did not receive any education or information in advance and there was no proper treatment. She had to stay in the hospital for weeks due to uncontrolled bleeding. She strongly feels that educating patients and parents on menstrual bleeding and on the psychosocial effects may prevent such negative healthcare experiences. She also emphasizes unrestricted use of factor concentrates to treat HMB, if needed, since this made a huge difference for her. Medical doctors in HTCs should be aware that HMB may be very stressful and anticipate better, in order to prevent a traumatic experience with lifelong impact.

3 | CASE 2

A 36-year-old carrier of severe haemophilia B, who has mild haemophilia herself (factor IX of 15 IU/dl), desires to get pregnant. The gene defect is unknown. Her father died from HIV, and there is no contact with other family members except for a younger sister who has never been tested either. The medical history includes HMB, bleeding after sexarche and an ovulation bleed. She was three times treated with clotting factor and uses a combined oral contraceptive pill to control menstrual bleeding and suppress ovulation. Difficulties with penetration, which arose after the negative experience at her sexarche, hamper conception.

3.1 | Question for the multidisciplinary team

The 25% of WBD report that they experience a severe impact on reproductive decision-making.[10] How should this woman be guided in conceiving, pregnancy and childbirth?

3.1.1 | Psychosexual therapist perspective

Good sex education is very important, underscored by the fact that girls who are more sexually autonomous have more pleasant and less unwanted sexual experiences.[16,17] In contrast to common opinion, adolescents who start their sexual careers well prepared tend to have their sexual debut at a later age than those who do not.[18] Health professionals who feel reluctant to talk about sex with their patients may be pleased to learn that the majority of patients are grateful that their healthcare provider initiates a conversation about sex.[19] A good heuristic is to first explain why you ask questions about sexuality (because sexual problems in people with this condition are common), then ask permission to talk about it (in young girls ask permission from the parents too), and be specific in your questioning using clear, non-obscuring language.

More than 25% of young women are familiar with pain during intercourse.[20] This pain is mostly caused by a lack of adequate sexual arousal in combination with a high pelvic floor muscle tone. Even though systematic data are lacking, it is likely that fear of bleeding, like any other fear, impairs sexual arousal and therefore increases the risk of bleeding.[21] Difficulties with sexual arousal and with penetrative sex require a multidisciplinary approach, taking into account all relevant biopsychosocial variables. In this particular case, an important question is as follows: Is there fear of pain or fear of bleeding? Does she have symptoms of PTSS related to excessive bleeding at coital debut, which impair sexual response? Are there other negative sexual experiences? Fear (of any kind) not only impairs sexual arousal but also increases the likelihood of having an increased pelvic floor muscle tone.[22] This patient's difficulties with vaginal penetration suggest that this is the case for her too. In that case, physical therapy may be indicated, but only in conjunction with treatment of the fear of bleeding or the PTSS, otherwise physical therapy is likely to be ineffective.

When complaints are severe or physical therapy is unhelpful, referral to a psychosexual therapist is in order. Discussing the role of sexual arousal and vaginal lubrication in the promotion of successful and pleasurable vaginal intercourse is important. To encourage the experience of sexual pleasure, it helps to relax her body and her pelvic floor, to pay attention to arousing and pleasurable bodily sensations, to eliminate all pressures to perform, and to not focus on intercourse as the only and final goal of sexual interactions. Encouragement to use lubricants to enable unaroused vaginal penetration is likely to exacerbate the sexual difficulties. Because she wants to become pregnant, she may be inclined to continuing attempts to engage in intercourse. A much more successful and healthy strategy is to separate the sexual problem from the wish to conceive, by instructing her and her partner to deliver sperm to the uterus on fertile days using a small syringe, while encouraging them to engage in arousing and pleasurable non-penetrative sexual activities.

3.1.2 | Geneticist perspective

Haemophilia follows an X linked recessive inheritance pattern (Figure 1). Affected men have a mutation in the factor 8 or factor 9 gene, which are both located on the X chromosome. Because men do not have a second X chromosome with a normal copy of the factor 8 or 9 gene (but a Y chromosome instead), they will not produce enough factor VIII or IX for normal coagulation and have symptoms of haemophilia. Daughters of male haemophilia patients are obligate carriers of haemophilia. Daughters of haemophilia carriers have a 50% chance of inheriting the X chromosome with the factor 8 or 9 mutation and are therefore potential carriers.

Haemophilia carriers (HCs) should be identified and genetically counselled, preferably before they become pregnant, to be able to

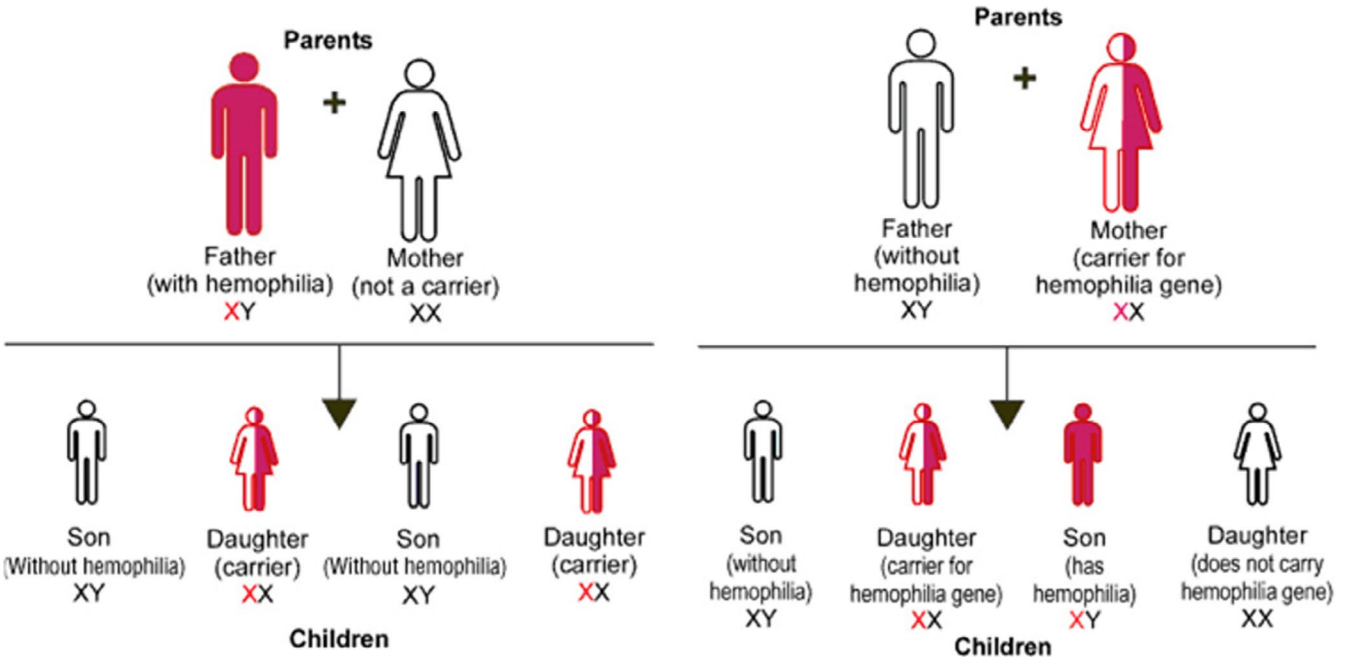

FIGURE 1 Genetics of haemophilia [Colour figure can be viewed at wileyonlinelibrary.com]

choose from all available reproductive options. Normal clotting factor levels in HCs *do not exclude* carriership of the familial haemophilia mutation. Carriership can be detected with direct DNA analysis if the familial mutation is known. In case the familial mutation is unknown, as in the presented case, DNA analysis to identify the familial mutation should preferably be done in a male family member affected with haemophilia or, if they are not available, an obligate carrier. Last choice is to primarily test a potential carrier, because of the (small) chance of failure to detect the culprit mutation in carriers due to technical reasons.[20]

There are several reproductive options for haemophilia carriers: no children or adoption, oocyte donation, preimplantation genetic diagnosis (PGD) and prenatal diagnosis (PND).

Preimplantation genetic diagnosis is an in vitro fertilization (IVF) treatment in which one single cell of an embryo is tested for gender or a known familial mutation. When using PGD for haemophilia, only female or unaffected male embryos are placed into the uterus to create a pregnancy. It is a reliable, but costly and time-consuming method to prevent having an affected child, with high emotional burden and a 25% chance of an ongoing pregnancy per IVF cycle in general.[23] Before or after birth, the absence of the familial mutation should be confirmed.

Prenatal diagnosis with the goal to terminate pregnancy in case of an affected boy is different from PND with the aim to guide obstetric management. For PND with the aim to terminate pregnancy, in case of an affected boy, a Y-PCR test in maternal blood can be done at around 9 weeks of gestation to determine the sex of the foetus. In case of a boy, chorionic villus biopsy is done around 11 weeks of gestation. There is a small chance of pregnancy loss with this procedure. In PND to guide obstetric recommendations, ultrasound for gender determination is done around 16 weeks gestation. In case of a boy, amniocentesis is performed around 30–32 weeks of gestation. In case of an affected boy or when parents choose no PND, an atraumatic delivery is indicated. In the near future, non-invasive prenatal diagnosis (NIPD) with genetic analysis on cell-free foetal DNA isolated from maternal blood will hopefully become available to enable early, reliable and safe prenatal diagnosis.[24]

3.1.3 | Haematologist perspective

The 30% of haemophilia carriers have clotting factor levels below 40 IU/dl and about a third experiences abnormal bleeding, although the bleeding tendency is not 1:1 related to the clotting factor level.[25,26] HMB and post-partum haemorrhages are the most frequent bleeding episodes seen associated with lower quality of life and iron deficiency anaemia.[7] When a carrier, who is on hormonal treatment because of heavy menstruation, has a wish to become pregnant she should be prepared for the possibility of HMB once this medication has been stopped. Tranexamic acid must be at home and the haemoglobin level and ferritin level should be checked before stopping hormonal treatment and repeated when heavy blood loss exists. Adequate levels of haemoglobin and ferritin should be maintained with oral and/or iv iron- ensuring they are adequate before pregnancy. It should also be checked whether DNA testing has been performed and the possibilities of PND and the modern treatment of haemophilia discussed, preferably in a multidisciplinary setting. Since haemophilia treatment has evolved greatly the past years, it is important to discuss the current treatment options and perspectives of having haemophilia, to prevent decisions being made solely based on negative family experiences with older haemophilia patients.[27]

This information has to be tailored according to the personal and family history of severe/moderate or mild haemophilia and repeated before each pregnancy. Clotting factor correction is required for invasive procedures like PND, PGD and chorion villus collection in case of a decreased FVIII or FIX level. During pregnancy, a physiologic increase in factor VIII levels occurs and levels should therefore be checked repeatedly in carriers of haemophilia A. However, in haemophilia B carriers, like the presented case, a rise in factor IX hardly occurs.[28] As there is a risk for maternal and neonatal bleeding, a proper pregnancy and delivery plan should be made in time, preferable before 32 weeks of gestation in case preterm delivery occurs, and communicated with the patient and other members of the multidisciplinary team. This plan should include discussing the need of clotting factor correction to prevent post-partum bleeding and measures to prevent bleeding in (possibly) affected male neonates, as well the type of painkillers and use of Tranexamic acid post-partum. In contrast to haemophilia A carriers, where desmopressin can be used in addition to factor replacement, unsatisfactory factor IX levels for delivery in haemophilia B carriers can only be corrected with factor IX concentrate. Instrumental delivery must be avoided to decrease maternal and neonatal (intracranial) bleeding risks and is contraindicated in case of a (possibly) affected boy. In moderate/severe haemophilia, invasive neonatal surveillance procedures are also contraindicated. Regional block anaesthesia is possible if factor levels are >50 IU/dl. When clotting factor levels are <50 IU/dl at 32–34 weeks of gestation, clotting factor correction is given to secure haemostasis during and after delivery. This should be repeated aiming for a through level >50 IU/dl for 3–5 days after vaginal delivery and 7–10 days in case of caesarean section.[29] The risk of intracranial bleeding in the neonate with haemophilia is 3.6% in countries with good quality of care. This is 40–80 times higher than non-affected neonates and is related to the way of delivery and awareness of carriership in mothers.[30,31] A multidisciplinary delivery plan is key to both mother and child.

3.1.4 | Patients' perspective

Anxiety occurs that prior traumatic experiences with HMB may return when contraceptives are stopped. Sexual problems are not easily discussed and it is much valued if healthcare providers offer an opening to start this conversation. WBD have to cope with feelings of guild towards their possible offspring which may inherit a severe disease they carry. Negative family experiences play an important role and may add to the anxiety, even causing her to decide not to have children if she is not well informed about the current health care perspectives. Support and guidance from the multidisciplinary team, starting in the phase of conception and onwards is required, especially in this case, since normal penetration in an issue. Taken together, many insecurities and uncertainties cause a lot of worry and difficulties in reproductive decision-making. A safe environment to openly discuss these issues with members the multidisciplinary team is imperative.

4 | CONCLUSION

Woman and girls with bleeding disorders may experience heavy menstruation from menarche onwards. This has physical, psychosocial and psychosexual impact which requires a patient-centred multidisciplinary approach. If a woman with an inherited bleeding disorder desires to become pregnant, preconception counselling is essential, to discuss genetic diagnosis, modern treatment for the bleeding disorder in question and possible choices to prevent having an affected child. Maternal bleeding risks during conception, delivery and the post-partum period should be anticipated and severe bleeding prevented by making personalized multidisciplinary plans. Adequate management and good education is best provided in HTCs by an experienced multidisciplinary team.

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CONFLICT OF INTEREST

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