

Gynaecological issues in women with bleeding disorders: CSL Behring Symposium

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The symposium focused on issues around surgery, ovulation bleeding, quality of life and pelvic pain in women with bleeding disorders. **Surgery:** Young women with congenital bleeding disorders, especially those with severe forms, are more likely to experience gynaecological and obstetric disorders than unaffected women. Surgery may be required to manage heavy menstrual bleeding (HMB), ovulatory bleeding, endometriosis and delivery. Major surgery should be undertaken only in hospitals with a haemophilia centre and 24-hour laboratory capability. Correction of haemostasis, either by desmopressin, coagulation factor or platelet transfusion, is essential for a successful outcome of surgery. Management of pregnancy requires a multidisciplinary approach;

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the mode of delivery is based on the consensus of gynaecologist and haematologist, and with respect to the patient's diagnosis. **Ovulation bleeding:** Women with bleeding disorders are at risk from excessive gynaecological bleeding associated with menstruation, ovulation, pregnancy and delivery. Ovulation bleeding is associated with the rupture of ovarian cysts and causes abdominal pain; complications include haemoperitoneum, fertility problems and ovarian torsion. Management includes hormonal and haemostatic therapies, in combination if necessary, and surgery as a last resort. Current management is based on experience in a relatively small number of cases and more clinical data are needed. **Health-related quality of life:** In addition to experiencing joint and tissue bleeds, women experience psychosocial and medical issues associated with menstruation, pregnancy, labour and delivery. Menorrhagia has the greatest impact, and is associated with impaired HRQoL in almost all and dissatisfaction with the burden of treatment. There is a need for focused psychosocial support and a specific tool for the assessment of HRQoL in women with bleeding disorders. **Pelvic pain:** Gynaecological causes of pelvic pain in women

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with bleeding disorders include dysmenorrhoea, mid-cycle pain, bleeding into the corpus luteum and endometriosis. There is no correlation between bleeding tendency and endometriosis severity; however, screening for a bleeding disorder should be considered. Pharmacological management may be hormonal or non-hormonal. Gonadotrophin-releasing hormone agonists offer an alternative to surgery for women with severe bleeding disorders who have endometriosis. Paracetamol is the preferred early analgesic option. Endometrial ablation controls heavy bleeding and pelvic pain but is not recommended for women with large fibroids or a large endometrial cavity. Hysterectomy is an option of last resort. Education for health professionals should include raising awareness about the management of pain in women with bleeding disorders.

Keywords: *Women with bleeding disorders, von Willebrand disease, factor VII deficiency, surgery, Slovakia, ovulation bleeding, health-related quality of life, pelvic pain, patient experience*

SURGERY IN WOMEN WITH VON WILLEBRAND DISEASE OR FACTOR VII DEFICIENCY

The recorded prevalence in Slovakia of von Willebrand disease (VWD) and, in particular, factor VII deficiency is among the highest in the world^[1]. Gynaecological problems are more common among young women with VWD and other bleeding disorders than unaffected women^[2,3]. Women with a bleeding disorder may need to undergo surgery for menorrhagia (dilatation and curettage, endometrial ablation, hysterectomy), ovulatory bleeding and endometriosis (laparoscopy, laparotomy, oophorectomy), and during delivery (Caesarean section). Women with VWD may also require surgery for gastrointestinal bleeding.

Treatment options

In women with VWD haemostasis can be achieved by administration of desmopressin or by von Willebrand factor (VWF) replacement. Non-replacement therapy with desmopressin results in release of endogenous VWF and secondary increase of FVIII. Responsiveness to desmopressin is assessed by measuring VWF and FVIII activity 60 minutes and four hours after administration. Monotherapy with desmopressin is appropriate only for persons with less severe forms of VWD and some basal production of VWF (Type 1 and some with Type 2A and 2N); it is ineffective in Type 3 and contraindicated in Type 2B VWD. Tachyphylaxis occurs after two to three days' continuous use, meaning that desmopressin is not suitable for longer term use. Some people may not tolerate desmopressin; adverse effects include flushing, fluid retention (fluid restriction is necessary), hyponatraemia and headache. Desmopressin should be avoided in children aged under two years and older people with cardiovascular disease. Patients unresponsive to desmopressin, and those undergoing major surgery or who are at risk of bleeding for a period longer than three days^[4] should receive replacement therapy. Currently, VWF concentrates derived from human plasma containing VWF/FVIII complex or pure VWF are available; recombinant VWF is under development. Longer term use of products with high FVIII content may lead to an undesirably high level of FVIII and risk of thrombosis.

Women with VWD should undergo major surgical procedures in hospitals with a haemophilia centre and 24-hour laboratory capability. The surgical team should include a haematologist and surgeon experienced in the management VWD, and there must be good communication between these specialists. VWF and FVIII should be monitored regularly during and after the procedure. The initial target for FVIII:C and VWF:RCo in women undergoing major surgery is ≥ 100 IU/dL; postoperatively the levels should be maintained at >50 IU/dL for ≥ 7 –10 days. The risk

Table 1. Dosage and monitoring recommendations for patients with VWD undergoing surgery^[4,6,7]

	MAJOR SURGERY	MINOR SURGERY
Loading dose VWF:RCo	40–60 IU/kg	30–60 IU/kg
Target level for surgery	VWF: RCo and FVIII 100 IU/dL	VWF: RCo and FVIII ≥ 80 IU/dL
Maintenance dose VWF:RCo	20–40 IU/kg every 8–24 hours	20–40 IU/kg every 12–24 hours
Sustained post-OP troughs of VWF: RCo and FVIII	>50 IU/dL for 7–14 days	>50 IU/dL for 3–5 days
Monitoring FVIII and VWF:RCo	troughs and peaks daily	trough and peak at least once
Safety parameter	VWF:RCo <200 and FVIII <200 –300 IU/dL	

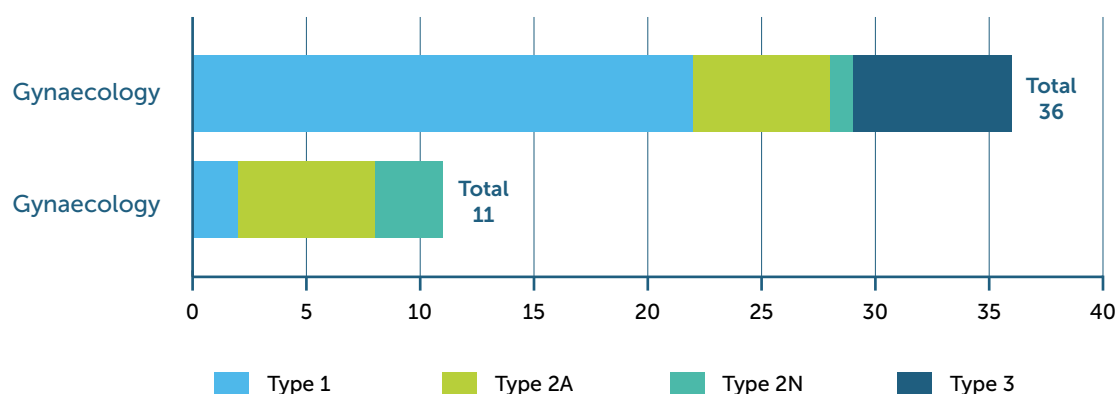


Figure 1A. Obstetric and gynaecological-related surgeries in women with VWD in Slovakia, 1998–2018

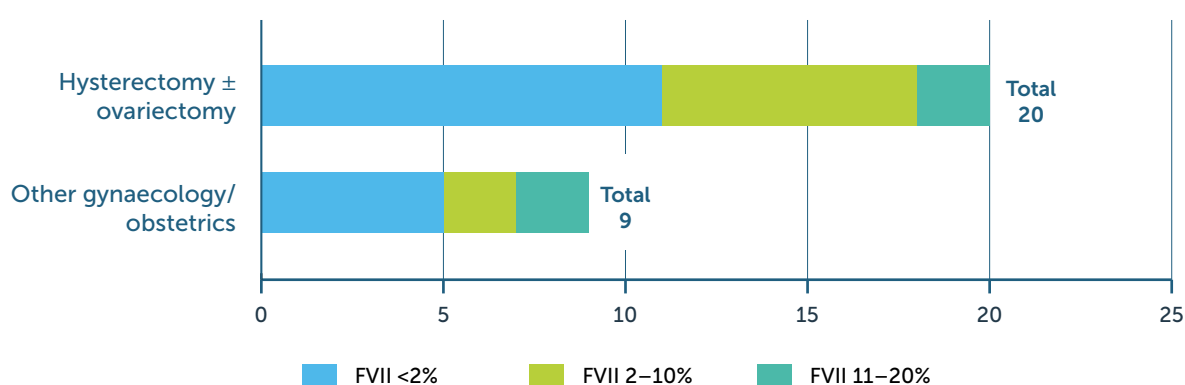


Figure 1B. Obstetric and gynaecological-related surgeries in women with FVII deficiency in Slovakia 1998–2019

of perioperative thrombosis can be minimised by maintaining VWF:RCo<200 IU/dL and FVIII <250 IU/dL^[5]. Table 1 summarises published recommendations for dosage and monitoring in patients with VWD undergoing major or minor surgery^[4,6,7]. Anticoagulation during replacement therapy should be considered for patients at high risk of thrombosis^[4]. In women with FVII deficiency and other rare bleeding disorders surgical procedures are performed under the missing coagulation factor or platelets replacement. Adjuvant therapy to promote haemostasis in women suffering from gynaecological problems includes fibrinolysis inhibitors (tranexamic acid) and hormonal therapy. In some surgical procedures also topical agents such a fibrin glue may be used.

Surgical experience in Slovakia

At the National Haemophilia Centre in Bratislava, Slovakia, 276 surgical procedures (113 major) were carried out in 125 persons with VWD (80 women) between 1998 and 2018. There were 47 procedures

for gynaecological and obstetric indications (Figure 1A). Consumption of VWF was greater for major than minor procedures, and greater and of longer duration in patients with a more severe bleeding disorder (rank order Type 1 < Type 2 < Type 3). Continuous infusion of VWF/FVIII concentrate used in five patients (four women) with VWD has been shown to maintain haemostatic levels of FVIII:C, vWF:Ag and vWF:Rco adequate for postoperative period^[8].

In the same period, 209 procedures (112 major) were carried out in 98 people (70 females) with congenital FVII deficiency. Ninety-eight procedures were performed in patients with severe FVII deficiency (FVII <2 IU/dL). Of 29 gynaecological or obstetric surgeries, 20 entailed hysterectomy+/- oophorectomy, and nine were procedures for other gynaecological or obstetric indications (Figure 1B); 16 procedures were performed in women with severe FVII deficiency. Either plasma-derived FVII or recombinant FVIIa were employed for factor replacement. Due to a short FVII half-life (four to six hours) FVII concentrates were administered every

six hours on days 1–4, reducing to every eight hours on days 5–7, and 12-hourly on days 8–10 in patients undergoing major surgery.

Delivery in women with bleeding disorders

The management of pregnancy and delivery requires a multidisciplinary approach and a management plan for delivery. Clotting factor levels should be measured in the third trimester of pregnancy (at 32–34 and 36 weeks' gestation). An adequate stock of factor concentrates should be ordered beforehand.

Prior to delivery, coagulation should be checked and factor level corrected to >50 IU/dL to cover regional anaesthesia and vaginal delivery. Vacuum extraction, forceps, foetal scalp electrodes and foetal sampling should all be avoided. Caesarean section should be considered at an early stage in the case of complications.

Some obstetricians recommend elective Caesarean section. The advantages of this approach include the ability to plan delivery and avoid an emergency section, a possibly lower risk of intracranial haemorrhage, and a lower risk of complications such as pelvic floor damage. Arguments against Caesarean section include marginal benefits compared with uncomplicated vaginal delivery, the need for surgical intervention, postoperative risk of thrombosis, an increased risk of placenta praevia and accreta, and Caesarean section requirement in subsequent pregnancy.

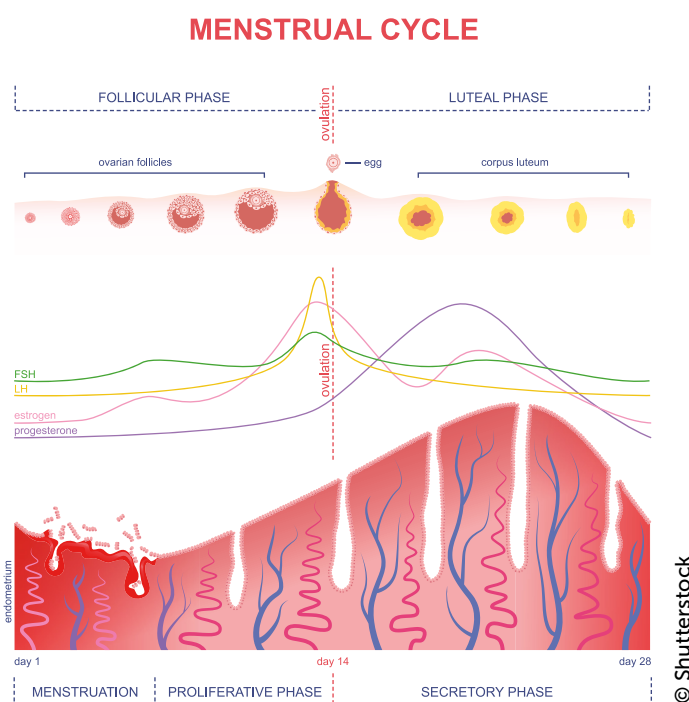
Replacement therapy for delivery should continue for five to six days. Each neonate should have an ultrasound scan to assess possible intracranial damage.

Summary

Today, any surgical procedure can be safely performed in a woman with a bleeding disorder with adequate preparation and suitably experienced personnel. Although there is a higher risk of surgery for gynaecological pathology, the types of procedures carried out in women with bleeding disorders are similar to those in the population as whole. All major surgery should be carried out in a unit with access to a treatment centre for bleeding disorders; only minor surgery can be performed in a regional hospital with the support of experienced specialists.

OVULATION BLEEDING IN WOMEN WITH A BLEEDING DISORDER

Ovulation bleeding is associated with the rupture of ovarian cysts, and occurs during the second week of the menstrual cycle, a time when cyclic variation



Ovulation bleeding occurs in up to 30% of women, but women with bleeding disorders are at risk from excessive bleeding. In a normal menstrual cycle, ovulation occurs during the second week, coinciding with a trough in the cyclic variation of von Willebrand factor.

causes a trough in VWF activity^[9]. (This cyclic variation in VWF is dampened in women taking a combined oral contraceptive.) Ovulation bleeding is also associated with abdominal pain. Complications include haemoperitoneum and fertility problems; large ovarian cysts may cause ovarian torsion.

Case studies

CASE 1

A 32-year-old woman with severe Type 1 VWD (VWF:RCo <15%, factor VIII 70%) underwent hysteroscopic removal of a missed abortion at six weeks' gestation in 2012. In 2014, she gave birth to a son; the delivery was uncomplicated and managed with tranexamic acid, desmopressin and uterotonics. In 2019 she presented to her GP with acute abdominal pain and was admitted as an emergency to the nearest hospital. Her haemoglobin level was 7.4 mmol/dL. The gynaecologist diagnosed ovulation bleeding and contacted the haemophilia treatment centre 12 hours later. She received three doses of VWF/factor VIII complex (Humate P). Despite this, her haemoglobin level was found to have fallen to approximately 6.1 mmol/dL. On the following

day, she underwent abdominal surgery with cover from VWF/factor VIII complex 12-hourly. A blood clot was removed from one ovary and the bleeding site was coagulated.

CASE 2

A 41-year-old woman with mild haemophilia A (factor VIII 30%, low VWF and platelet dysfunction due to medication) had two children at age 20; both deliveries were uncomplicated. In 2018, she underwent hysterectomy for heavy menstrual bleeding as she could not tolerate hormonal therapy. The outcome of surgery was complicated by infection, vaginal bleeding and bladder atonia, which she continues to manage with catheterisation. She experienced monthly midcycle abdominal pain for which she self-treated with VWF/factor VIII complex when self-testing confirmed ovulation had occurred. In 2019, she was admitted to hospital with ovulation bleeding that occurred after a double ovulation; she was too ill to self-treat. The gynaecologist was initially doubtful that she needed treatment with a clotting factor, but she was successfully treated with VWF/factor VIII complex. She is now considering hormonal treatment despite having had a hysterectomy.

Discussion

Several case reports of ovulation bleeding have been published^[10-17]. Surgery, including in some cases oophorectomy, was usually but not always necessary in addition to medication to control bleeding. One published case report of a 35-year-old woman with Glanzmann's thrombasthenia describes the serious challenge of stopping bleeding^[15]. She had experienced recurrent corpus luteum rupture since 2004 and had twice undergone surgery. Attempts to control her bleeding included treatment with the combined oral contraceptive, on-demand platelet transfusion, oral tranexamic acid, recombinant factor VIIa and leuporelin acetate. In 2010, she was admitted to hospital with abdominal pain, tenderness and distention associated with intra-abdominal bleeding due to corpus luteum rupture. Bleeding was not controlled by almost 24 units of platelet concentrate, 90 µg/kg rFVIIa two-hourly and massive red blood cell transfusions. Surgery was therefore impossible, but bleeding was eventually controlled by paracentesis and intraperitoneal infusion of tranexamic acid. She slowly improved

over the next two months, but was readmitted three months later with abdominal distension and poor nutritional status. There was no alternative to surgery covered by plasmapheresis, factor VIIa and platelet transfusion. Nine litres of fluid were drained from a giant haematoma, and total abdominal hysterectomy with bilateral salpingo-oophorectomy was carried out. Histological examination revealed a haemorrhagic ovarian cyst, granulation tissue on the cyst wall, haematoma and endometriosis in the uterine serosa.

More usually, ovulation bleeding can be controlled medically. Measurement of luteinising hormone can be useful when investigating recurrent mid-cycle pain. Treatment options include pain management and the combined oral contraceptive to suppress ovulation. The levonorgestrel-releasing intrauterine device Mirena does not prevent ovulation and therefore will not prevent bleeding. Non-hormonal options include dual therapy with desmopressin and oral tranexamic acid^[18]. Clotting factor can be used on demand or when ovulation is expected; prophylaxis is a further option. Surgery, including oophorectomy, is indicated when pharmacological interventions fail to control bleeding and oophorectomy.

In conclusion, there is a need to educate women with bleeding disorders about the importance of seeking advice from their treatment centre if they experience mid-cycle pain. Treatment should aim to suppress ovulation, but timely clotting factor replacement is indicated for women contemplating pregnancy. Surgery should be reserved until medical management is exhausted; however, if hysterectomy is under consideration to control heavy menstrual bleeding, women with ovulation bleeding may also consider ovariectomy. Current management is based on experience in a relatively small number of cases and more clinical data are needed.

QUALITY OF LIFE IN RELATION TO GYNAECOLOGICAL BLEEDING

Many women with a bleeding disorder are undiagnosed, misdiagnosed or untreated. The lack of awareness around women with bleeding disorders adds to their sense of isolation. Women, like men, experience joint and tissue bleeds; however, unlike men, they also have psychosocial and medical issues associated with menstruation, pregnancy, labour and delivery. Having a bleeding disorder means that a woman's experience of these events is different from that of their peers, but they commonly face a lack of adequate support in all aspects of their lives, including their families, the

healthcare system and employers. Without appropriate and sensitive intervention, the issues experienced by women experiencing psychosocial difficulties can result in undesirable emotional and physical outcomes. Initiatives such as the National Hemophilia Foundation's 'Victory for Women' (V4W / victoryforwomen.org) in the United States are aimed at addressing some of the critical issues faced by women with bleeding disorders.

Menorrhagia has the greatest impact on women with bleeding disorders, affecting family life, work life, physical and psychological health and social life, and raising practical difficulties. It is estimated that 18 million women worldwide consider their menstrual bleeding to be excessive and 10% of these meet the criterion for menorrhagia^[19]. Perhaps 90% of cases of menorrhagia are associated with an underlying bleeding disorder, which is undiagnosed in 5–24% of women and 5–36% of adolescents^[20]. The prevalence of menorrhagia in women with VWD is 74–92%^[21]; 58% of women with VWD say that menorrhagia is the most frequent type of bleeding they experience^[22]. Improving health-related quality of life (HRQoL) is an important goal in the management of menorrhagia, and in women with bleeding disorders, assessing their HRQoL would help to better understand what life is like for

them, identify specific healthcare needs and treatment strategies, and deliver appropriate care. Menorrhagia is often present from the onset of menarche, but the diagnosis of a bleeding disorder is often delayed until women are in their thirties – in one series of women with VWD the median delay was 16 years^[23] – and delayed diagnosis affects HRQoL.

Women with VWD who have pain during menstruation report impaired HRQoL in almost all domains compared with those who report no or little pain. In one Swedish study of women with VWD (13% Type 3), half had heavy periods but almost all perceived limitations on life activities due to menstruation (Figure 2) and scored lower than the general population for the domain 'bodily pain'^[24]. There is wide overlap between different types of VWD in their impact, but Types 2 and 3 tend to be associated with greater impairment. Endometrial ablation has been shown to improve HRQoL for women both with and without a bleeding disorder^[25,26].

There is strong evidence that HRQoL is impaired by having a bleeding disorder, and accurate knowledge of the impact of menorrhagia on HRQoL would help to both individualise treatment and assess the magnitude of any change^[27]. A study of women with heavy or irregular

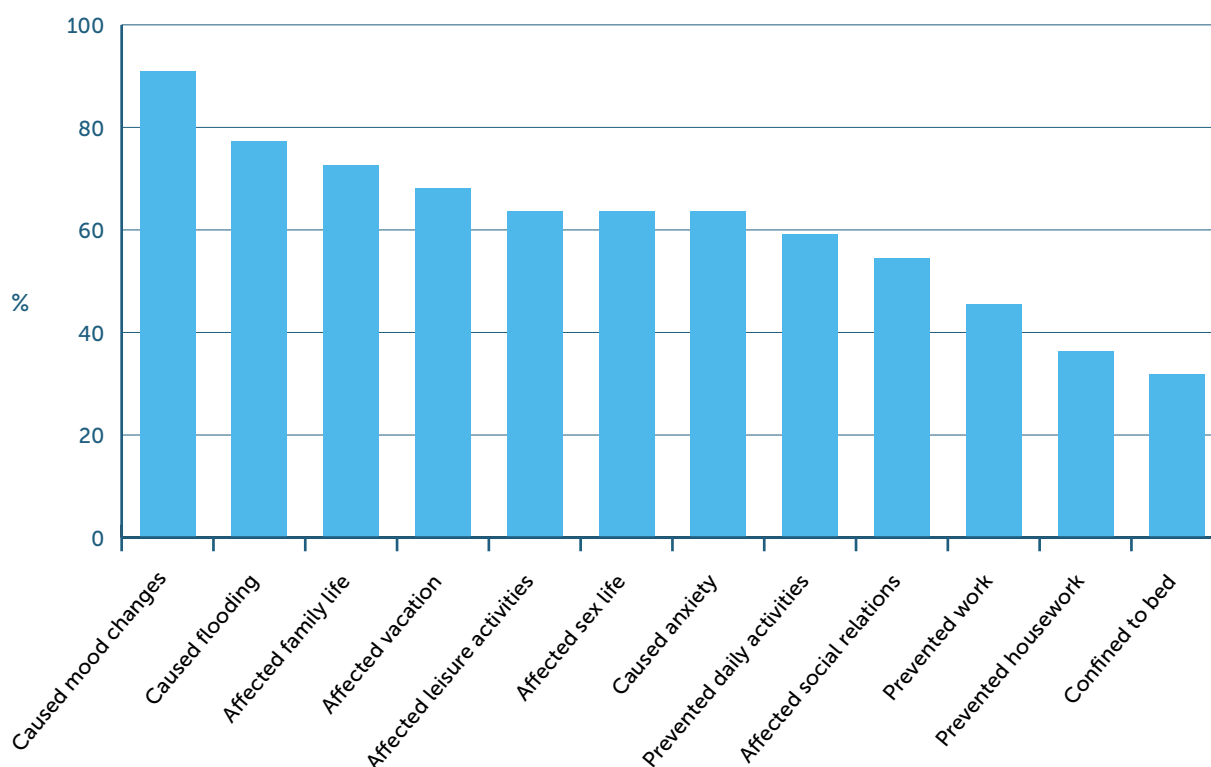


Figure 2. Impact of heavy menstrual bleeding on overall life activities in women with von Willebrand disease (% affected, n=22)^[23]

uterine bleeding identified important themes, including bleeding-associated pain, self-consciousness, social embarrassment and ritual-like behaviour – however, they also reported that, when answering questions about bleeding and quality of life, the questions failed to go into enough depth to adequately characterise their experience^[28]. Other studies have looked at HRQoL in women with bleeding disorders using questionnaires including general health daily activities, dysmenorrhoea, quality of life during menstruation^[29], and more specifically at the impact of menstruation in women and with bleeding disorders on the activities of daily living and lifestyle^[30,31]. However, some studies have not used validated instruments to measure HRQoL. Studies such as WisH-QoL in France, a five-year prospective study of HRQoL and treatment satisfaction in people with VWD, show the value of using a disease-specific HRQoL questionnaire^[21]. An interim analysis of 140 participants (95 female) showed that women of childbearing age reported HRQoL impairment associated with their treatment, their attitude to VWD and their hopes of the future. They also reported dissatisfaction with their treatment burden. However, while the validated VWD-specific HRQoL questionnaire includes the specific dimension ‘menstruation’ for women^[32], there is no validated instrument to specifically assess the impact of menorrhagia on HRQoL in women with a bleeding disorder.

In conclusion, there is growing interest in the impact of bleeding disorders on HRQoL in women with bleeding disorders, and evidence shows that HRQoL in women with bleeding disorders is generally impaired due to menorrhagia. A number of generic instruments are available for the assessment of HRQoL, but disease-specific evaluation of HRQoL and treatment satisfaction enables deeper insight into patients’ experience, their perception of wellbeing and their specific healthcare needs. To best support women with bleeding disorders in their HRQoL and the challenges they face, psychosocial programmes should be made available to address critical issues and provide support. Most HRQoL studies in women with bleeding disorders have used generic instruments; there is a need to develop a specific tool with greater discriminatory power.

PAIN MANAGEMENT IN WOMEN WITH RARE BLEEDING DISORDERS – FOCUS ON PELVIC PAIN

Pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain perception is influenced

by psychological factors such as stress and anxiety and moderated by attention and distraction. It is therefore highly variable and unique. Acute and chronic pain may occur simultaneously.

Pelvic pain in women with bleeding disorders

Gynaecological causes of pelvic pain in women with bleeding disorders are more frequent than in the general population, such as dysmenorrhoea (reported by 50–86%), mid-cycle pain due to ovulation bleeding and peritoneal irritation (30–74%), and bleeding into the corpus luteum (7–14%); and others that occur with a similar frequency, such as endometriosis (2–10%)^[20,33]. However, although endometriosis is not more prevalent among women with a bleeding disorder, the diagnosis is made more frequently in this group because they are more likely to come to medical attention.

The bleeding associated with endometriosis deposits is exacerbated by primary haemostatic defects, causing more pain. Endometriosis is associated with increased platelet count (due to chronic inflammation) and abnormal platelet aggregation. There is no correlation between bleeding tendency and endometriosis severity, but it is recommended that screening for a bleeding disorder should be considered for women diagnosed with endometriosis^[33].

Pain management

Interventions to manage pain may be non-pharmacological, pharmacological or surgical. None of the non-pharmacological options (including cognitive behaviour therapy, physiotherapy, acupuncture and hypnosis) are supported by evidence of effectiveness.

Pharmacological approaches may be hormonal or non-hormonal. Hormonal options include the combined oral contraceptive (COC), the levonorgestrel intrauterine device Mirena, progestogens, gonadotrophin-releasing hormone agonists (GnRHAs). It is safe to use COCs continuously to reduce the frequency of menstruation and control menstruation-associated pain, depending on patient preference^[34,35].

Mirena reduces menstrual bleeding and dysmenorrhoea, and reduces pelvic pain associated with endometriosis; it is effective in perimenopausal women who have irregular, heavy periods^[36]. Unlike a copper intrauterine device, it does not reduce activity of factor VIII in the endometrium. However, the risk of expulsion or malposition in women with a bleeding disorder is 15%, higher than in other women, perhaps due to heavier menstrual flow and uterine contractions. Other disadvantages include increased

risk of ovarian cyst, which affects all women but may be associated with haemorrhagic cysts in women with bleeding disorders [37,38].

GnRHAs offer an alternative to surgery for women with severe bleeding disorders who have endometriosis, but they are not indicated primarily for heavy menstrual bleeding due to the risk of adverse effects. They cause ovarian suppression and amenorrhoea, and can be combined with a COC or the synthetic oestrogen tibolone.

The range of non-hormonal treatment options includes drugs widely used in the management of bleeding disorders. Tranexamic acid reduces endometrial tissue plasminogen activator and plasmin activity in the menstrual and peripheral blood in women with heavy menstrual bleeding. The effectiveness of desmopressin alone is doubtful, but it is effective in combination with tranexamic acid [39-41].

There is little evidence to guide the choice of analgesic for pelvic pain. One US survey of patients with haemophilia found the most frequently used agents were NSAIDs and paracetamol, though a significant minority used opioid-based analgesics such as hydrocodone [42]. Based on a survey of 22 European haemophilia treatment centres, a consensus statement recommended paracetamol as the first-line analgesic for adults with acute or chronic pain, adding a weak opioid, an NSAID (COX-2 selective agents are contraindicated in people with cardiovascular risk factors), or tramadol or a strong opioid if earlier steps do not control pain [43].

Other medication includes antispasmodics to relieve pain associated with uterine contractions.

Surgical options

Endometrial ablation can now be offered on an outpatient basis and is effective in controlling heavy bleeding and pelvic pain; however, it is not recommended for women with large fibroids or a large endometrial cavity. Other approaches include oophorectomy, which can be carried out laparoscopically, and uterine artery embolisation. Hysterectomy is an option of last resort; when indicated, removal of the ovaries should be considered, in which case hormone replacement therapy should be offered.

Summary

In summary, the management of pelvic pain is multifactorial and there is no clear consensus about what constitutes an optimal approach. Every person's experience of pain is unique. Personalised treatment

plans should involve a specialist pain team, and women with inherited bleeding disorders should have access to a multidisciplinary clinic. Education for health professionals should include raising awareness about the management of pain in women with bleeding disorders.

PREPARING FOR SURGERY – THE PATIENT PERSPECTIVE

Evelyn Grimberg drew on her personal experience of living with Glanzmann's thrombasthenia to shed light on the challenges faced by women with bleeding disorders when they need surgery. She had been admitted for emergency surgery at the age of 16 and had been unable to prepare for the operation. She felt uninformed about the effects of hormone therapy to prevent ovulation and her expectations of the outcome of her care did not match those of her gynaecologist. Her experience is not unusual. Accounts from other women who have described similar experiences show that uncertainty and anxiety are common (Table 2).

Surgery is best approached as a team effort that includes the woman herself, the surgeon, anaesthetist, haematologist and the treatment centre. A woman should be her own champion and expert patient: surgeons probably know less than she does about her bleeding disorder. She should feel in good shape. She should have good people around who can provide



Evelyn Grimberg, who has Glanzmann's thrombasthenia, advocates a team approach to preparing for surgery for women with bleeding disorders. The woman herself should be involved, alongside the surgeon, anaesthetist, haematologist and her treatment centre.

Table 2. Women's personal experiences of surgery

"I need surgery and got my treatment plan. This one is different from the last one. I'm worried if everything will go well"	"Surgery went well, but I had a bleed afterwards when I was back home. I got hospitalised again"	"My physician was too scared of bleeds during surgery, so he decided not to perform surgery"	"I had surgery but they didn't consult my haematologist"	"They almost gave me painkillers with blood thinners"
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support and speak on her behalf when she is unable to speak for herself. She should know what to expect from physicians and the process of hospitalisation, and what they want the admission and procedure to achieve. She should be aware of what is happening – if surgery is not being carried out at a hospital with a treatment centre, the staff at the treatment centre should be informed and involved. She should check whether there is a treatment plan; if there is already a treatment plan in place, a copy should be taken to the hospital where surgery is being performed, so that the surgical team understands what treatment is necessary to prevent bleeds and manage pain before, during and after the operation. Having a specialist haemophilia nurse present to administer factor replacement is very reassuring. It is important to check that any medication prescribed is appropriate and safe for someone with a bleeding disorder. It is routine to prescribe an anticoagulant to prevent postoperative thrombosis and staff may need to be reminded – preoperatively – that this is contraindicated in someone with a bleeding disorder.

As Evelyn found, preparation is not always possible. When emergency surgery is necessary, the treatment centre should be informed and the procedure should be carried out at a hospital with a treatment centre where possible. While wearing a bracelet with details of diagnosis is a personal decision, it can be invaluable for health professionals. Similarly, it is important to carry medical details and contact information for your treatment centre in a bag or wallet, including the name and number of who to contact in an emergency.

DISCUSSION

The audience sought to clarify some of the points made in the presentations. The panel was asked to explain why intrauterine devices are associated with a higher risk of ovarian cysts. Although the reason is not clear, it may be caused by incomplete suppression of ovarian function. Cysts that are less than 5cm in diameter do not warrant surgery and are not an indication that the device should be removed. Polycystic ovarian syndrome, which is associated with multiple small cysts,

is not associated with the cysts that may occur in a woman with a bleeding disorder.

Thinking about Evelyn's emphasis on personal responsibility when preparing for hospital admission, the panel was asked to comment on where the balance of responsibility lies between the patient and the surgical team. They agreed that an individual should have a voice but cannot be expected to bear responsibility for the medical and surgical aspects of her care. In all cases, the relevant treatment centre should be involved as early as possible.

The role of assessing HRQoL as part of managing bleeding disorders was raised. The panel agreed that women can almost always benefit from psychological input. A comprehensive care centre should provide access to a psychologist, though smaller centres may find this difficult.

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REFERENCES

1. World Federation of Hemophilia. Report on the Annual Global Survey 2017. October 2018. Available from <http://www1.wfh.org/publications/files/pdf-1714.pdf> (accessed 20 June 2019).
2. Bevan JA, Maloney KW, Hillery CA, et al. Bleeding disorders: A common cause of menorrhagia in adolescents. *J Pediatr* 2001; 138: 856-61.
3. Batorova A, Jankovicova D, Prigancova T, et al. Abstract 32FP03: Management of surgery in congenital factor VII deficiency. In: Abstracts of the XXIXth International Congress of the World Federation of Hemophilia, Buenos Aires, Argentina, 10-14 July 2010. *Haemophilia* 2010; 16 (Suppl 4): 1-158. doi: [10.1111/j.1365-2516.2010.02283.x](https://doi.org/10.1111/j.1365-2516.2010.02283.x).

KEY MESSAGES

- Women with a bleeding disorder are at risk from excessive gynaecological bleeding associated with menstruation, ovulation, pregnancy and delivery
- Women with a bleeding disorder should seek advice from their treatment centre if they experience mid-cycle pain
- Any surgical procedure can be safely performed in a woman with a bleeding disorder with adequate preparation and suitably experienced personnel. Major procedures should preferably be undertaken in a hospital with a treatment centre
- The management of pelvic pain is multifactorial. Every person's experience of pain is unique and there is no clear consensus about what constitutes an optimal approach
- Women with a bleeding disorder should play an active role in planning their surgery and should be supported by their treatment centre

- Miesbach W, Berntorp E. Von Willebrand disease – the 'Dos' and 'Don'ts' in surgery. *Eur J Haematol* 2017; 98: 121-27. doi: 10.1111/ejh.12809.
- White G. Current treatment guidelines – experience from the USA. In: Berntorp E, Peake I, Budde U, et al. Von Willebrand's disease: a report from a meeting in the Åland islands. *Haemophilia* 2012; 18 Suppl 6: 1-13. doi: 10.1111/j.1365-2516.2012.02925.x.
- Tuohy E, Litt E, Alikhan R. Treatment of patients with von Willebrand disease. *J Blood Med* 2011; 2: 49-57. doi: 10.2147/JBM.S9890.
- Curnow J, Pasalic L, Favaloro EJ. Treatment of von Willebrand disease. *Semin Thromb Hemost* 2016; 42: 133-46. doi: 10.1055/s-0035-1569070.
- Bátorová A, Martinowitz U. Continuous infusion of coagulation factors. *Haemophilia* 2002; 8: 170-77.
- Kadir RA, Economides DL, Sabin CA, et al. Variations in coagulation factors in women: effects of age, ethnicity, menstrual cycle and combined oral contraceptive. *Thromb Haemost* 1999; 82: 1456-61.
- Bottini E, Pareti FI, Mari D, et al. Prevention of hemoperitoneum during ovulation by oral contraceptives in women with type III von Willebrand disease and afibrinogenemia. Case reports. *Haematologica* 1991; 76: 431-3.
- Meschengieser SS, Alberto MF, Salviú J, et al. Recurrent haemoperitoneum in a mild von Willebrand's disease combined with a storage pool deficit. *Blood Coagul Fibrinolysis* 2001; 12: 207-9.
- Payne JH, Maclean RM, Hampton KK, et al. Haemoperitoneum associated with ovulation in women with bleeding disorders: the case for conservative management and the role of the contraceptive pill. *Haemophilia* 2007; 13: 93-7.
- Girolami A, Lombardi AM, Candeo N, et al. Control of ovulation-induced hemoperitoneum by oral contraceptives in a patient with congenital hypoprothrombinemia and in another with congenital factor V deficiency. *Acta Haematol* 2008; 119: 236-40. doi: 10.1159/000141782.
- Cetinkaya SE, Pabuccu EG, Ozmen B, Dokmeci F. Recurrent massive hemoperitoneum due to ovulation as a clinical sign in congenital afibrinogenemia. *Acta Obstet Gynecol Scand* 2011; 90: 192-4. doi: 10.1111/j.1600-0412.2010.01034.x.
- Buyukasik Y, Boyraz G, Selcuk I, et al. Giant abdominopelvic haematoma arising from ovulation in a Glanzmann's thrombasthenia patient with platelet refractoriness: treatment with surgery and intra-abdominal tranexamic acid. *Acta Haematol* 2012; 128: 154-7. doi: 10.1159/000339085.
- Terzic M, Likic I, Pilic I, et al. Conservative management of massive hemoperitoneum caused by ovulation in a patient with severe form of von Willebrand disease – a case report. *Clin Exp Obstet Gynecol* 2012; 39 :537-40.
- Özdemir Ö, Sarı ME, Kurt A, et al. Recurrent massive haemoperitoneum associated with ruptured corpus luteum in women with congenital afibrinogenemia; case report. *Turk J Obstet Gynecol* 2014; 11: 242-45. doi: 10.4274/tjod.04935.
- Davies J, Kadir RA. Heavy menstrual bleeding: An update on management. *Thromb Res* 2017; 151 Suppl 1: S70-S77. doi: 10.1016/S0049-3848(17)30072-5.
- Smith H. Menorrhagia. *S Afr Pharm J* 2013; 80: 16-8.
- James AH, Kouides PA, Abdul-Kadir R, et al. Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. *Am J Obstet Gynecol* 2009; 201: 12.e1-8. doi: 10.1016/j.ajog.2009.04.024.
- Borel-Derlon A, Goudemand J, Desprez D, et al. Wish-QoL Study – Assessment of health-related quality of life (HRQoL) and health-economic aspects in patients with von Willebrand disease (VWD) in France: results of the women cohort. *Blood* 2016 128: 1395.
- Scharrer I. Women with von Willebrand disease. *Haemostaseologie* 2004; 24: 44-9.
- Kirtava A, Crudder S, Dilley A, et al. Trends in clinical management of women with von Willebrand disease: a survey of 75 women enrolled in haemophilia treatment centres in the United States. *Haemophilia* 2004; 10: 158-61.
- Govorov I, Ekelund L, Chaireti R, et al. Heavy menstrual bleeding and health-associated quality of life in women with von Willebrand's disease. *Exp Ther Med* 2016; 11: 1923-29. doi: 10.3892/etm.2016.3144.
- El-Nashar SA, Hopkins MR, Barnes SA, et al. Health-related quality of life and patient satisfaction after global endometrial ablation for menorrhagia in women with bleeding disorders: a follow-up survey and systematic review. *Am*

- J Obstet Gynecol* 2010; 202: 348.e1-7. doi: 10.1016/j.ajog.2009.11.032.
26. Rubin G, Wortman M, Kouides PA. Endometrial ablation for von Willebrand disease-related menorrhagia – experience with seven cases. *Haemophilia* 2004; 10: 477-82.
 27. Kadir RA, Edlund M, von Mackensen S. The impact of menstrual disorders on quality of life in women with inherited bleeding disorders. *Haemophilia* 2010; 16:832-9. doi: 10.1111/j.1365-2516.2010.02269.x.
 28. Matteson KA, Clark MA. Questioning our questions: do frequently asked questions adequately cover the aspects of women's lives most affected by abnormal uterine bleeding? Opinions of women with abnormal uterine bleeding participating in focus group discussions. *Women Health* 2010; 50: 195-211. doi: 10.1080/03630241003705037.
 29. Kadir RA, Sabin CA, Pollard D, Lee CA, Economides D. Quality of life during menstruation in patients with inherited bleeding disorders. *Haemophilia* 1998; 4: 836-41. doi: 10.1046/j.1365-2516.1998.00208.x.
 30. Kouides PA, Phatak PD, Burkart P, et al. Gynaecological and obstetrical morbidity in women with type 1 von Willebrand disease: results of a patient survey. *Haemophilia* 2000; 6: 643-8.
 31. Kirtava A, Drews C, Lally C, Dilley A, Evatt B. Medical, reproductive and psychosocial experiences of women diagnosed with von Willebrand disease receiving care in haemophilia treatment centres: a case-control study. *Haemophilia* 2003; 9: 292-7. doi: 10.1046/j.1365-2516.2003.00756.x.
 32. Von Mackensen S, Federici A. Quality of life assessment in patients with von Willebrand's disease: development of a first disease-specific instrument (VWD-QoL). *Haemostaseologie* 2007; 1: 126.
 33. Byams VR, Kouides PA, Kulkarni R, et al. Surveillance of female patients with inherited bleeding disorders in United States Haemophilia Treatment Centres. *Haemophilia* 2011; 17 Suppl 1: 6-13. doi: 10.1111/j.1365-2516.2011.02558.x.
 34. Hillard PA. Menstrual suppression: current perspectives. *Int J Womens Health* 2014; 6: 631-7. doi: 10.2147/IJWH.S46680.
 35. Kadir RA, James AH. *Reproductive Health in Women with Bleeding Disorders*. World Federation of Hemophilia, Treatment of Hemophilia Monographs, no. 48, 2009. Available at <http://www1.wfh.org/publication/files/pdf-1206.pdf> (accessed 11 July 2019).
 36. Bayer LL, Hillard PJ. Use of levonorgestrel intrauterine system for medical indications in adolescents. *J Adolesc Health* 2013; 52(4 Suppl): S54-8. doi: 10.1016/j.jadohealth.2012.09.022.
 37. Lukes AS, Perry S, Ortel TL. Von Willebrand's disease diagnosed after menorrhagia worsened from levonorgestrel intrauterine system. *Obstet Gynecol* 2005; 105: 1223-6.
 38. Rimmer E, Jamieson MA, James P. Malposition and expulsion of the levonorgestrel intrauterine system among women with inherited bleeding disorders. *Haemophilia* 2013; 19: 933-8. doi: 10.1111/hae.12184.
 39. Kadir RA, Lee CA, Sabin CA, et al. DDAVP nasal spray for treatment of menorrhagia in women with inherited bleeding disorders: a randomized placebo-controlled crossover study. *Haemophilia* 2002; 8: 787-93.
 40. Edlund M, Blombäck M, Fried G. Desmopressin in the treatment of menorrhagia in women with no common coagulation factor deficiency but with prolonged bleeding time. *Blood Coagul Fibrinolysis* 2002; 13: 225-31.
 41. Kouides PA, Byams VR, Philipp CS, et al. Multisite management study of menorrhagia with abnormal laboratory haemostasis: a prospective crossover study of intranasal desmopressin and oral tranexamic acid. *Br J Haematol* 2009; 145: 212-20. doi: 10.1111/j.1365-2141.2009.07610.x.
 42. Witkop M, Lambing A, Kachalsky E, et al. Assessment of acute and persistent pain management in patients with haemophilia. *Haemophilia* 2011; 17: 612-9. doi: 10.1111/j.1365-2516.2010.02479.x.
 43. Holstein K, Klamroth R, Richards M, et al. Pain management in patients with haemophilia: a European survey. *Haemophilia* 2012; 18: 743-52. doi: 10.1111/j.1365-2516.2012.02808.x.

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