

REPRODUCTIVE HEALTH IN WOMEN WITH BLEEDING DISORDERS

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Reproductive Health in Women with Bleeding Disorders

Rezan A. Kadir and Andra H. James

Introduction

Bleeding disorders can result from thrombocytopenia, platelet function disorders, abnormal collagen (such as in Ehlers-Danlos syndrome), and clotting factor deficiencies, including a deficiency of von Willebrand factor (VWF). Bleeding disorders may be acquired or inherited. Mild inherited bleeding disorders are common, while severe inherited bleeding disorders are rare, affecting as few as one in 5,000 to one in 1,000,000 people [1].

Hemophilia is the commonest severe bleeding disorder. Hemophilia A (factor VIII deficiency) and B (factor IX deficiency) are X-linked disorders that together affect one in 5,000 men. Women are affected as carriers of hemophilia. Carriers may also have low factor levels and experience significant bleeding symptoms [2]. 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 to affect women and men. Two large prospective epidemiological studies reported a 0.8-1.3% prevalence of mild VWD in the general population [3, 4]. However, women are more likely to be symptomatic due to the bleeding challenges of menstruation and childbirth. This monograph will review the common obstetric and gynecological challenges in women with bleeding disorders and their management.

Menorrhagia

Menorrhagia, or heavy menstrual bleeding, is the most common symptom that women with bleeding disorders experience. 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 [5].

Most of the data about the prevalence of menorrhagia in women with bleeding disorders come from reports of women with VWD. The prevalence of menorrhagia in these reports ranges from 74-92% [6-8]. Women with VWD are five times more likely to experience menorrhagia than women without the


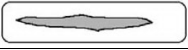

condition [9]. With respect to other bleeding disorders, the prevalence of menorrhagia in women with severe platelet dysfunction has been reported to be 51% in women with Bernard-Soulier syndrome [10] and 98% in women with Glanzmann thrombasthenia [11]; 59% in women with factor XI deficiency [12]; 57% in carriers of hemophilia [6]; and 35-70% in women with other rare factor deficiencies [13].




In addition to heavy menstrual loss, women with bleeding disorders also suffer from prolonged bleeding (more than seven days), excessive passage of large clots, and flooding during menstruation [6]. Adolescent girls and perimenopausal women may suffer the most, as menstrual cycles are often anovulatory (i.e. no egg is released) during these reproductive stages. This leads to irregular shedding of the endometrium and predisposes to increased and prolonged menstrual bleeding. Perimenopausal women are also more likely to have pelvic pathology, such as fibroids and endometriosis, which increase the risk of bleeding and the magnitude of menstrual problems.

Clinical assessment of menorrhagia

The only way to get an accurate measurement of menstrual blood loss is to assess hemoglobin content using the alkaline hematin method, a complex and expensive laboratory test. Since it is not feasible to use in clinical practice, the pictorial blood assessment chart (PBAC) has been used as a semi-objective alternative [14]. The PBAC (seen in Figures 1 and 2) consists of a series of diagrams representing lightly, moderately, and heavily soiled towels and tampons. The numbers at the top of the chart represent the days of the menstrual cycle. Women are instructed to mark the appropriate box each time a towel and/or tampon is discarded, after comparing its degree of saturation with those depicted on the chart. Passage of clots and episodes of flooding are also recorded. Lightly stained towels or tampons obtain a score of 1, moderately stained towels or tampons a score of 5, completely soaked tampons a score of 10, and completely soaked towels a score of 20. A total score of greater than 100 per cycle has been shown to be a reasonably good predictor of menstrual blood loss of more than 80 mL [14].

Figure 1: Assessment of menstrual blood loss using the pictorial blood assessment chart (PBAC)

Patient name:			Date of birth: DD/MM/YY			Date of start: DD/MM/YY		
Towel	1	2	3	4	5	6	7	8
								
								
								
Clots / Flooding (small/large)								

Tampon	1	2	3	4	5	6	7	8
								
								
								
Clots / Flooding (small/large)								

Score: _____

Scoring system

Towels

- 1 point For each lightly stained towel
- 5 points For each moderately soiled towel
- 20 points If the towel is completely saturated with blood

Tampons

- 1 point For each lightly stained tampon
- 5 points For each moderately soiled tampon
- 10 points If the tampon is completely saturated with blood

Clots

- 1 point For small clots (½ inch)
- 5 points For large clots (1 inch)

Flooding

- 5 points For any episode of flooding

A drawback of the chart is that it must be completed prospectively and results are not available at the time of an initial evaluation. Additionally, the validity of the chart and its ease of use have been questioned by some investigators [15, 16]. Nonetheless, the PBAC is a simple and inexpensive tool and has been used successfully to monitor response to treatment [17, 18].

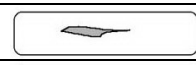
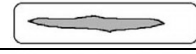




In most situations, practitioners must rely on menstrual history and clinical impression. Variables that can best predict a menstrual blood loss of more than 80 mL are passage of clots greater than one inch (2.5 cm) in diameter, low ferritin (according to the investigators'

laboratory reference), or the need for changing a pad or tampon more than hourly (flooding) [19]. The presence of these features in the menstrual history may help identify women who suffer from heavy menstrual bleeding.

Assessment of bleeding disorders in women with menorrhagia

Menstruation is an important hemostatic challenge that can be associated with excessive bleeding in the presence of any hemostatic defect. Therefore, menorrhagia can be the presenting symptom of a bleeding disorder (especially in its mild form) in otherwise

Figure 2: Assessment of menstrual blood loss using the pictorial blood assessment chart (PBAC): Example of a completed chart

Patient name: Jane Smith			Date of birth: 14/03/1978			Date of start: 25/08/2006		
Towel	1	2	3	4	5	6	7	8
	//	/	/		/	/		
			///	//				
		//	//					
Clots / Flooding		½" x 3	1" x 1					
Tampon	1	2	3	4	5	6	7	8
		/			//	/		
		//	///	//				
		/	////					
Clots / Flooding								

Score: 208

asymptomatic women. Women with bleeding disorders commonly present with adolescent menorrhagia, typically at menarche – the first hemostatic challenge for these young girls.

The prevalence of VWD in women presenting with menorrhagia is reported to be 13% (95% confidence interval 11-16%), according to a systematic review of 11 studies including 988 women [20]. The data on the prevalence of platelet dysfunction in women presenting with menorrhagia are very limited but it has been reported to be as high as 47% [21]. Other less common inherited bleeding disorders have also been identified in women presenting with menorrhagia, such as carriers of hemophilia, factor XI deficiency, and other rare bleeding disorders. Therefore, menorrhagia should alert clinicians to the possibility of a bleeding disorder.

A full hematological evaluation is not necessary and not practical for all women with menorrhagia. Clinicians should take a thorough bleeding history and consider testing in the presence of:

- Menorrhagia since menarche
- Family history of a bleeding disorder
- Personal history of one, but usually several, of the following symptoms:
 - Epistaxis (generally bilateral epistaxis, > 10 minute duration once in the last year, possibly necessitating packing or cautery)

- Notable bruising without injury (and > 2 cm in diameter)
- Minor wound bleeding (i.e. from trivial cuts lasting for > 5 minutes)
- Bleeding in the oral cavity or gastrointestinal tract without an obvious anatomic lesion
- Prolonged or excessive bleeding following dental extraction
- Unexpected post-surgical bleeding
- Recurrent midcycle pain due to ovulation bleeding
- Hemorrhage requiring blood transfusion
- Postpartum hemorrhage, especially secondary postpartum hemorrhage (after 24 hours).
- Failure to respond to conventional management of menorrhagia and prior to any surgical intervention for menorrhagia.

In patients whose symptoms warrant further investigation, the initial hematological assessment should include:

- Full blood count/complete blood cell count
- Blood group
- Ferritin level
- Activated partial thromboplastin time (aPTT)
- Prothrombin time (PT)
- Assessment of VWF (measured with ristocetin cofactor activity and antigen) and FVIII levels.

If the initial hemostatic tests are normal, platelet function (aggregation and release) tests should be performed if available. Further hemostatic assessment, including specific coagulation factor profile, is considered on the basis of the degree and severity of personal bleeding symptoms and family history.

Other Gynecological Conditions

Dysmenorrhea

Dysmenorrhea (painful periods) is a common gynecological complaint for all women, but women with bleeding disorders more commonly suffer from period pain. Moderate to severe dysmenorrhea has been reported in half of these women [6, 7]. Treatment would usually involve non-steroidal anti-inflammatory drugs (NSAIDs), but these should be avoided in women with bleeding disorders due to the drugs' antiplatelet activity. Alternative analgesia such as acetaminophen or paracetamol and codeine-based products may be used. The combined oral contraceptives may also help reduce dysmenorrhea, as may the levonorgestrel intrauterine system (Mirena® IUS) (see "Hormonal therapy" below).

Hemorrhagic ovarian cysts

When a woman ovulates, a small amount of bleeding may occur with rupture of the follicle and formation of the corpus luteum. This may be associated with abdominal and pelvic pain (known as *Mittelschmerz*, a German word that means "middle pain"). Women with bleeding disorders are more likely to have significant bleeding at ovulation with resulting pain, hemorrhagic ovarian cysts, broad ligament hematomas, or even hemoperitoneum (significant bleeding into the abdominal and pelvic cavity). There have been many case series of hemorrhagic ovarian cysts in women with inherited bleeding disorders, with a prevalence ranging from 2-25% [13].

Although these gynecological complications can be treated surgically, conservative management with the use of appropriate hemostatic agents (tranexamic acid, desmopressin, and coagulation factor replacement) is advisable in women with bleeding disorders [22]. Combined oral contraceptives suppress ovulation and have been successfully used to prevent recurrences.

Endometriosis and other gynecological conditions

Endometriosis is a painful condition in which endometrial tissue, the tissue which lines the uterus,

implants in the pelvic cavity and organs outside of the uterus. There are several possible reasons why women with bleeding disorders would be more likely to be diagnosed with endometriosis. Although there is disagreement regarding the cause of endometriosis, the prevailing theory is that it results from retrograde menstruation (the backward flow of menstrual blood). Heavy menstrual bleeding is a risk factor for retrograde menstruation and endometriosis. Women with bleeding disorders have heavier menstrual bleeding, more retrograde menstruation and, possibly, more endometriosis. Another possible explanation is that women with bleeding disorders are more likely to experience symptomatic bleeding from the implantation of endometrial tissue.

There is no strong evidence that women with bleeding disorders are more likely to develop endometriosis, fibroids (leiomyoma), polyps, or endometrial hyperplasia (excessive growth of lining of the uterus), but in a survey by the U.S. Centers for Disease Control of 102 women with VWD, these gynecological problems were more commonly reported by affected women compared to the controls [23]. Since most of these pathologies often present with bleeding, women with bleeding disorders are more likely to be symptomatic and therefore diagnosed.

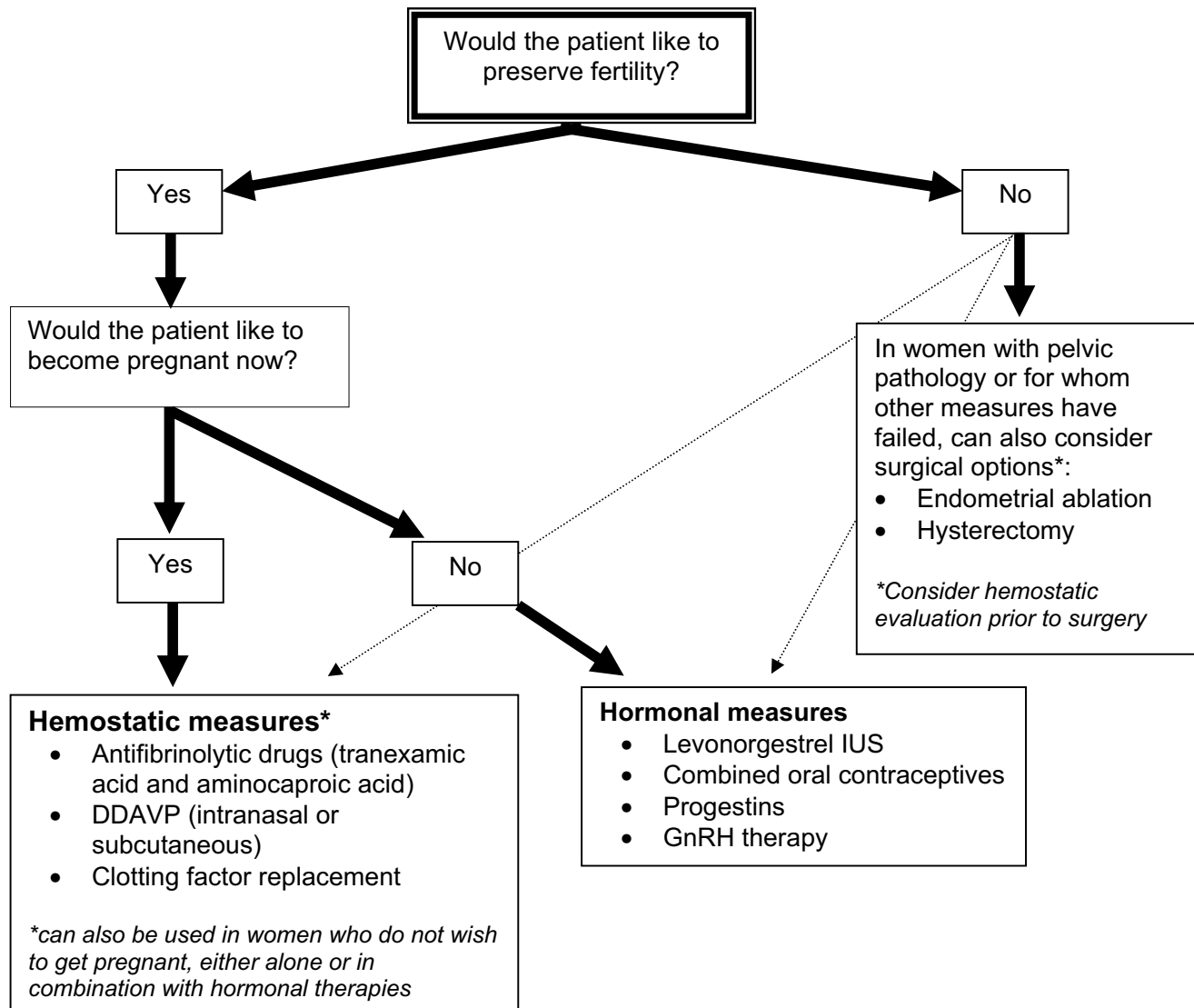
Management of Menorrhagia in Women with Bleeding Disorders

Since abnormal bleeding may be a sign of a gynecological problem other than a bleeding disorder, a full gynecological evaluation is required prior to treatment of menorrhagia [5, 24]. With the exception of NSAIDs, which affect platelet function and systemic hemostasis [25] and are not generally prescribed for patients with bleeding disorders [26], other gynecologic treatment options may be suitable depending on the woman's age, gynecological conditions, and reproductive plans (see Figure 3 for treatment algorithm).

Hormonal therapy

Levonorgestrel intrauterine system

The levonorgestrel intrauterine system (LNG-IUS, Mirena®) is the most effective medical treatment for menorrhagia [27] and has been shown to be useful for reducing menstrual blood loss in women with bleeding disorders [17, 28]. It is also an effective and reversible method of contraception, making it an

Figure 3: Algorithm of management of menorrhagia

ideal treatment for women with menorrhagia who wish to preserve their fertility. The licensed duration of its use is five years in many countries. However, effective and safe extended use of the same LNG-IUS for up to eight years has been reported [29, 30]. This gives a long grace period before replacing the system, which is especially important for women living in areas where medical care is not readily available.

The main problem with the LNG-IUS is irregular bleeding or spotting, especially in the first three to six months of use, leading to discontinuation of treatment. Proper counselling and patient education may increase tolerance. In women with inherited

bleeding disorders, there is a potential risk of bleeding at the time of insertion and hemostatic coverage may be required.

Combined hormonal contraceptives

Combined hormonal contraceptives reduce menstrual blood loss by thinning the endometrium and possibly by increasing factor VIII and VWF levels. Combined hormonal contraceptive methods currently available include the combined oral contraceptive (COC) pill, transdermal contraceptive patches, and vaginal rings. They provide reliable birth control and cycle control and reduce dysmenorrhea and other menstrual complaints. In women with bleeding disorders, they

have an added advantage of controlling ovulation bleeding and midcycle pain. Continuous use of these therapies (rather than the traditional 21-day course) is safe and can be used to control timing and frequency of menstruation as well as menstruation-associated symptoms [31]. This can be very useful for girls and women with severe menstrual problems that interfere with school/work attendance and performance. Serious side effects of hormonal contraceptives include hypertension, liver dysfunction, and thrombosis. Women with bleeding disorders, however, may have a low inherited thrombotic risk. Other side effects include nausea, headache, breast tenderness, breakthrough bleeding, skin reactions, and depression.

Oral progestogens

Oral progestogens such as medroxyprogesterone acetate and norethisterone are recommended treatments for menorrhagia when used as a 21-day course (days 5-26). Shorter courses such as luteal phase progesterone treatments are not effective. Compliance is usually poor with oral progestogens due to side effects such as fatigue, mood changes, weight gain, bloating, depression, and irregular bleeding. In high doses, oral progestogens can be used with DDAVP or clotting factor to treat acute menorrhagia in women with bleeding disorders.

Progestin-only contraceptives

Progestin-only contraceptives such as Depo-Provera[®] (medroxyprogesterone acetate) injections, progestin-only pills, and the Implanon[®] implant also reduce endometrial proliferation and may reduce menstrual blood loss or suppress menstruation, but they are associated with a high rate of irregular bleeding and spotting. Insertion of the Implanon[®] implant could also cause bleeding in women with bleeding disorders and might require preventative treatment with a hemostatic agent.

Medroxyprogesterone acetate is now also available in a subcutaneous formulation, depo-subQ provera 104[™], providing an alternative to the intramuscular formulation, which can result in intramuscular bleeding in a woman with a severe bleeding disorder.

Gonadotropin-releasing hormone (GnRH) analogues

These drugs stop ovulation and are effective for reducing menstrual flow and duration. Hypoestrogenic side effects (such as hot flashes and a reversible loss of bone density) and cost prohibit their long-term

use, but GnRH analogues may be an alternative option to surgery for young women with resistant menorrhagia or severe bleeding disorders. If used for more than six months, hormone replacement therapy should be added to counteract low estrogen levels.

Hemostatic therapy

Hemostatic therapies have been reported to be effective in controlling menorrhagia in women with bleeding disorders. Hemostatic therapies include DDAVP (1-desamino-8-D-arginine vasopressin), a synthetic vasopressin that stimulates the release of VWF from endothelial cells, antifibrinolytic medications (tranexamic acid and aminocaproic acid), and coagulation factor concentrates. Hemostatic agents constitute the main treatment option for women who are trying to conceive, though they are also used in women who do not wish to get pregnant, either alone or in combination with hormonal therapy.

Oral tranexamic acid (1g, 3-4 times a day during the menstrual period) is usually well tolerated but side effects include nausea, headache, and diarrhea. DDAVP can be given by intravenous or subcutaneous injection or intranasally as a spray. For management of menorrhagia, it is usually administered as a nasal spray (150-300 mcg daily for a maximum of 3-4 days, usually during days with the heaviest blood flow). Side effects are related to a vasomotor effect and include tachycardia, flushing, and headache. With repeated doses there is a small risk of hyponatremia and water intoxication due to an antidiuretic effect. Therefore, fluid restriction during treatment is essential. Both tranexamic acid and DDAVP alone or in combination have been reported to be effective in controlling menorrhagia in women with bleeding disorders [18].

Clotting factor replacement may be required to control menorrhagia as regular prophylaxis in some women with severe factor deficiencies not responding to other treatments.

Surgical treatment

Surgery may be required in the presence of pelvic pathology and for women who do not tolerate medical treatment or in whom this is unsuccessful. Women with inherited bleeding disorders are more likely to have bleeding complications both peri-operatively and delayed (7-10 days later), even with relatively minor procedures such as hysteroscopy and biopsy.

Therefore, any surgical intervention should be performed in a centre with available laboratory support and an experienced hematologist. Prophylactic treatment may be required pre-operatively to reduce the risk of excessive bleeding.

Surgical options include hysterectomy and endometrial ablation. Both these procedures eliminate the possibility of future fertility and are reserved only for women who do not wish to have children.

Hysterectomy

Hysterectomy is a major surgical procedure and carries risks of serious morbidity and death. A mortality rate of 0.38 per 1000 [32], an operative complication rate of 3.5% (3% severe), and a post-operative complication rate of 9% (1% severe) have been reported [32, 33]. Hemorrhage is the most common complication [33]. Others include genitourinary complications, infection, and wound healing problems. The procedure requires a lengthy post-operative recovery period and carries a risk of long-term complications, including early ovarian failure and urinary and sexual problems. Peri-operative bleeding complications are of specific concern in women with bleeding disorders.

Therefore, hysterectomy should not be a first-line treatment but used only when other treatments fail or when pelvic pathology indicates its use in women who no longer wish to retain fertility.

Endometrial ablation

Endometrial ablation techniques are now widely used as an alternative to hysterectomy. There is some evidence of their effectiveness in reducing menstrual blood loss in women with bleeding disorders, as in other women [34]. These are minimally invasive procedures with a shorter operating time, recovery time, and complication rate when compared to hysterectomy. First generation techniques (resection, laser, and rollerball) are performed under hysteroscopic control. Second generation techniques are mostly performed blindly and involve the use of energy (heat, cold, or microwave) to ablate the full thickness of the endometrium. These techniques are simpler and faster to perform, while patient satisfaction scores and reduction in menstrual blood loss are similar. They can also be performed under local anesthetic [35]. As second generation techniques are less invasive with fewer bleeding complications, they may be more suitable for women with inherited bleeding disorders. However, sophisticated and expensive machines are necessary, which limits

their availability, especially for women in developing countries.

Management of acute adolescent menorrhagia

In these cases every effort should be made to preserve future fertility. Control of acute menorrhagia is usually achieved by a combination of hemostatic agents and high doses of hormonal therapy. Besides factor concentrates and intravenous antifibrinolytic medications, recombinant factor VIIa (if available) can be tried and has been used successfully in patients with severe platelet dysfunction disorders [36]. Platelet transfusions may also be required in cases of severe thrombocytopenia or platelet dysfunction.

Hormonal therapies to control the acute episode of menorrhagia include a single intravenous dose of 25 mg of conjugated equine estrogen (Premarin®). This has been shown to be effective in the treatment of acute, heavy menstrual bleeding [37]. In women whose bleeding has not stopped within three hours, the dose can be repeated every four hours, to a maximum of 48 hours. Oral conjugated equine estrogen can also be used. Large doses of estrogen promote regeneration of the endometrium, increase levels of coagulation factors (including FVIII and VWF), and promote platelet aggregation. An antiemetic should be given at the same time, as severe nausea and vomiting is very common with high doses of estrogen. Treatment with these high estrogen doses should also be followed by treatment with progestins (medroxyprogesterone acetate or norethisterone) or combined hormonal contraceptives to prevent recurrence.

GnRH analogues such as leuprolide acetate or goserelin acetate injected subcutaneously have been used to temporarily suppress menstruation in women at risk of severe, acute menorrhagia due to thrombocytopenia [38, 39].

Local measures may be required in unmanageable bleeding that does not respond to the above treatments. Examination under general anesthesia, evacuation of blood clots from the uterine cavity, and endometrial curetting should be considered. An inflated Foley balloon can be used to block the bleeding within the uterine cavity [40]. Packing the uterus has also been used to control acute menorrhagia in a young girl [41]. If the facilities are available, uterine artery embolization can be considered as a life-saving measure and last resort to avoid hysterectomy, but the long-term effects of this procedure on fertility

are not clearly known. It has been reported to successfully control acute menorrhagia in a 12 year-old female with deficiency of plasminogen activator inhibitor during her first menstrual period [42].

Girls and adolescents with known bleeding disorders should be counselled prior to menarche and have a plan in place for the possibility of acute, severe menorrhagia, which could occur with their first or any subsequent menstrual period. The plan should be made by the gynecologist and hematologist, in conjunction with the patient and her family. Because of the increased risk of transfusion, girls and adolescents who have not already should be immunized against hepatitis A and hepatitis B [43].

Pregnancy in Women with Bleeding Disorders

Preconception counselling

Women suspected of having a bleeding disorder or of being a carrier should undergo diagnostic testing before getting pregnant to allow for appropriate preconception counselling and early pregnancy management. This is most important for women with severe bleeding disorders or those who could potentially carry a severely affected baby, such as carriers of hemophilia.

Preconception counselling has two benefits:

1. It provides women and their family with adequate information on the genetic implications of their disorder, the available reproductive choices, and options for prenatal diagnosis.
2. It allows planning for pregnancy and establishing how and where the pregnancy can best be managed. Other aspects of preconception care include immunization against hepatitis A and B for those likely to require blood transfusion and general advice such as folic acid supplementation. A DDAVP test dose can also be carried out to assess response.

Psychological support should be available during all aspects of counselling, with an understanding of the ethnic and cultural influences on each individual. Women should also be offered the opportunity to speak with a pediatric hematologist regarding the care of a potentially affected child.

Prenatal diagnosis (PND)

PND is primarily considered in carriers of hemophilia because of the severity of the disorder in male offspring and because many affected families are already aware of the genetic defect. In each pregnancy, carriers of hemophilia have a 50% chance of having a male child that is affected and a 50% chance of having a female child that is a carrier. In other bleeding disorders, prenatal diagnosis is considered only when the fetus is at risk of being affected with severe forms of the disorder. Since most bleeding disorders are autosomal recessive, this risk is more common in families and cultures with high rates of consanguineous marriage.

Definitive PND can only be obtained with invasive prenatal diagnostic methods, such as chorionic villus sampling (CVS), amniocentesis, and cordocentesis. Unfortunately, these procedures are associated with a risk of miscarriage/fetal loss. CVS is the method most widely used today for the prenatal diagnosis of inherited bleeding disorders. It is performed at 11-14 weeks gestation under ultrasound guidance. It has the advantage of earlier diagnosis compared to amniocentesis, which is performed at 15-20 weeks gestation. Both are associated with an approximately 1% risk of miscarriage. Cordocentesis (ultrasound-guided fetal blood sampling) is performed at around 18-20 weeks gestation to obtain fetal blood for a clotting factor assay. The risk of fetal loss is higher with this procedure compared to amniocentesis or CVS. It is rarely performed today and may be an option for cases in which the causative mutation cannot be identified. Women at risk for severe bleeding should receive prophylaxis prior to any invasive procedure.

Fetal sex determination can be useful in the management of pregnancies at risk of hemophilia. It can be done easily and accurately by ultrasound from the second trimester. This can be reassuring to the parents when the fetus is female, and invasive testing can then be avoided. It will also enable the management plan for labour and delivery to be refined to avoid instrumental deliveries and invasive monitoring techniques in male fetuses, which have a 50% chance of being affected.

Pre-implantation genetic diagnosis is a relatively new technique. Embryos created using in vitro fertilization (IVF) are tested to identify those that are unaffected by the bleeding disorder, and these are

then selectively transferred to the uterus. This can eliminate the difficult decision of whether to terminate an affected pregnancy. There have been reports of its success recently in carriers of hemophilia [44]. This method will likely become a realistic option for some individual cases in the near future. However, further evidence on its efficacy and safety is still required. The cost and stress associated with IVF also need to be considered.

Antenatal management

Normal pregnancy is accompanied by increased concentrations of several coagulation factors including VIII, VWF, and a pronounced increase in fibrinogen [45]. There is also reduced fibrinolytic activity secondary to increased levels of plasminogen activator inhibitors, especially during the third trimester [45]. All of these changes contribute to the hypercoagulable state of pregnancy and, in women with bleeding disorders, to improved hemostasis. Despite this improvement, however, women with bleeding disorders often do not achieve the same levels of clotting factors that other women do and, therefore, are still at an increased risk of bleeding complications.

There are several case reports and case series documenting a profound increase in the risk of miscarriage and placental abruption resulting in fetal loss or preterm delivery in women with deficiencies of fibrinogen or factor XIII [46]. Factor replacement is recommended and used to reduce the risk of miscarriage and fetal loss in these women [46, 47].

The risk of miscarriage, antepartum bleeding, and adverse outcome in women with other bleeding disorders is less clear. Approximately 20% of all pregnancies are complicated by at least one bleeding episode, so bleeding in pregnancy may not be due to an underlying bleeding disorder. Obstetric causes should not be overlooked in these women.

Management of labour and delivery

Women at risk for severe bleeding should ideally be referred for prenatal care and delivery to a centre where, in addition to specialists in high-risk obstetrics, there is a hemophilia treatment centre or a hematologist with expertise in hemostasis. Laboratory, pharmacy, and blood bank support is essential. The management of childbirth will depend on the needs of the mother and her potentially affected infant at the time of delivery.

Prior to delivery, all women with bleeding disorders should have the opportunity to meet with an anesthesiologist. There is no consensus on the factor levels that are safe for regional anesthesia, but if levels are at least 50% and the rest of the coagulation studies are normal, regional anesthesia may be considered safe.

At the beginning of labour, maternal blood samples should be taken for blood group and serum saved for cross-matching, full blood count, and coagulation screen. It is often difficult to obtain factor levels during labour and is therefore acceptable to use third trimester levels to formulate an appropriate plan. However, the assessment and monitoring of relevant clotting factor levels are essential for those with low third trimester factor levels. If the factor level is low, intravenous access should be established and prophylactic treatment administered [48].

Desmopressin (DDAVP) may be used to raise factor VIII and von Willebrand factor levels in carriers of hemophilia A and women with VWD prior to invasive procedures. It is generally thought to be safe for mother and fetus, but care must be taken in its administration at the time of childbirth. DDAVP causes fluid retention and patients receiving DDAVP should be fluid-restricted, yet women commonly receive intravenous fluid during childbirth. They may also receive oxytocin for induction or augmentation of labour and after delivery to prevent postpartum hemorrhage. Oxytocin also causes fluid retention. At the time of childbirth, administration of DDAVP, combined with fluids and oxytocin, may result in life-threatening hyponatremia. Therefore, fluid balance and electrolyte levels should be strictly monitored.

The fetus is also at risk of bleeding complications during the process of birth. Invasive intrapartum monitoring techniques (e.g. fetal scalp electrode, fetal blood sampling) and instrumental deliveries (ventouse, midcavity or rotational forceps) should be avoided in pregnancies with potentially affected fetuses, as serious head bleeding may result from these procedures. Normal vaginal delivery is not absolutely contraindicated in these pregnancies, but prolonged labour should be avoided and delivery achieved by the least traumatic method. Although cesarean section may not completely eliminate the risk of serious neonatal bleeding complications [49], early recourse to cesarean section should be considered to minimize the risk of neonatal bleeding complications. Low forceps delivery may be considered less traumatic

than cesarean section when the head is deeply engaged in the pelvis and an easy outlet delivery is anticipated. Delivery in these cases needs to be performed by an experienced obstetrician [50].

A cord blood sample should be collected from neonates at risk of moderate or severe inherited bleeding disorders to assess coagulation status and clotting factor levels. This enables the identification and early management of newborns at risk of bleeding complications. If delivery has been traumatic or if there are clinical signs suggestive of head bleeding, a cranial ultrasound should be performed. It is also advisable to consider prophylactic cover in these cases. Intramuscular injections should be avoided in neonates at risk until the coagulation status is known. Vitamin K may be given orally and routine immunizations given intradermally or subcutaneously. If vitamin K is given intramuscularly (IM), apply firm pressure to the site for five to ten minutes. Heel sticks should also have pressure applied for five minutes and close observation of the site for 24 hours. Any surgical procedures (e.g. circumcision) should be delayed until the coagulation status of the neonate is known.

When assessing neonatal clotting factor levels, it should be appreciated that the levels of vitamin K-dependent factors (FII, FVII, FIX, and FX) correlate with gestational age due to liver immaturity and reach adult levels at six months of age. It is therefore not reliable to diagnose mild forms of inherited bleeding disorders at birth. Hemophilia A (FVIII deficiency), however, can be diagnosed at birth.

Postpartum management

After the delivery, the elevated coagulation factors return to pre-pregnancy levels. Therefore, the main risk of bleeding is after miscarriage or delivery. Postpartum hemorrhage (PPH) is a major cause of maternal morbidity and mortality, especially in developing countries and rural settings. It accounts for an estimated 140,000 maternal deaths each year worldwide and many more suffer from the long-term and debilitating consequences of the resultant anemia. While the most common causes of PPH are uterine atony (inefficient uterine contractility), retained placenta or placenta pieces, and genital tract trauma, coagulation disorders are recognized causes of PPH [51].

Women with bleeding disorders are at risk of primary (blood loss of more than 500 mL in the first 24 hours

after delivery) and secondary (excessive bleeding occurring between 24 hours and six weeks post-delivery) PPH, especially those with severe disorders [46]. Perineal/vaginal hematoma are rare complications of vaginal birth, but are also more likely to occur in women with bleeding disorders, especially after operative vaginal deliveries [13, 52].

Reducing the risk of PPH

PPH often occurs in women with low factor levels, and more severely. Therefore, prophylactic replacement therapy is recommended to cover labour, delivery, and the immediate postpartum period (at least three to four days for vaginal delivery and five to seven days for cesarean section) in these women. Table 1 shows the hemostatic levels required for delivery in women with inherited bleeding disorders. Available treatment options [53] are listed in Table 2. When treatment is required, recombinant products, if available, should be regarded as the products of choice to avoid the potential risk of viral transmission.

Active management of the third stage of labour is associated with a significant reduction in blood loss during childbirth and should be used in women with inherited bleeding disorders. It entails the administration of prophylactic uterotonics (agents that increase uterine muscle contractility), early cord clamping, and controlled traction of the umbilical cord. Misoprostol (200–400 mcg) is an inexpensive prostaglandin E1 analogue and uterotonic that can be given orally, sublingually, or rectally. It can be administered by non-medical birth attendants and has no special requirement for transport or storage. Therefore, it is a promising uterotonic for the prevention of PPH, especially in developing countries where most deliveries happen in rural settings. Its administration can be associated with side effects including vomiting, diarrhea, fever, and shivering.

In the event of an operative delivery, meticulous surgical hemostasis should be practiced to minimize blood loss. Care must also be taken to minimize maternal genital and perineal trauma, as women with inherited bleeding disorders are at particular risk of developing perineal hematoma [52, 54–55].

Since the pregnancy-induced increase in coagulation factors returns to pre-pregnancy levels within 14 to 21 days of delivery, women with bleeding disorders are particularly vulnerable to delayed or secondary postpartum hemorrhage during this time.

Table 1: Hemostatic levels for invasive procedures during pregnancy and for delivery

Inherited bleeding disorder	Clotting factor (activity)	Hemostatic levels, suggested (IU/dL) ¹	Normal range (non-pregnant) (IU/dL)	Comments
VWD	VWF	50	50 – 175	
Carrier of hemophilia A	FVIII	50	50 – 150	
Carrier of hemophilia B	FIX	50	50 – 150	
Fibrinogen deficiency	Fibrinogen	1.0 - 1.5 ²	2.0 - 4.0	To maintain >1.0 g/L during pregnancy
FII deficiency	FII	20 – 30	50 – 150	
FV deficiency	FV	15 – 25	50 – 150	
FVII deficiency	FVII	10 – 20	50 – 150	
FX deficiency	FX	10 – 20	50 – 150	
FXI deficiency	FXI	20 – 70	70 – 150	
FXIII deficiency	FXIII	20 – 30	70 – 150	To maintain >3 IU/dL during pregnancy

¹ For general guidance only. Personal and family bleeding history must be taken into consideration when deciding the need for prophylaxis. Please refer to text.

² g/L

Oral tranexamic acid can be used for the prevention and management of secondary PPH. Combined oral contraceptive pills, if not contraindicated, are also an option for preventing excessive bleeding in the late postpartum period.

It is important not to overlook the obstetric risk factors and causes of PPH in women with inherited bleeding disorders. In case of hemorrhage, after the initial assessment and restoration of circulatory volume, local causes should be excluded and replacement of the clotting factor should be performed. Management of PPH in these women presents a particular challenge and close collaboration between hematologists, obstetricians, and anesthesiologists is imperative.

Impact of Bleeding Disorders on Women

Bleeding disorders have a significant impact on women's health and quality of life [56, 57]. Women with bleeding disorders suffer reduced quality of life that negatively affects their academic, professional, and social life. Long-lasting menorrhagia leads to iron deficiency anemia, with all its consequences on physical and mental wellbeing. Many women are not aware that their symptoms are abnormal and do

not seek medical advice. Even when they do seek help, diagnosis of bleeding disorders is often overlooked and appropriate treatment is not provided due to lack of awareness among caregivers. Women with bleeding disorders are therefore more likely to have unnecessary surgical intervention, including hysterectomy, at an early age. Hysterectomy is a major operation with a significant risk of complications, especially in developing countries with limited medical resources. In many of these women, bleeding disorders are only suspected and diagnosed after the hysterectomy, when they develop bleeding complications.

Medical care for women is lacking in many countries around the world. There may be cultural taboos and obstacles preventing women from seeking help, particularly for menstrual problems. Heavy and prolonged menstrual bleeding and pain may lead to marital disharmony and possibly fertility problems. These are often seen as a failure for the woman, further compromising her mental and psychological wellbeing. In some developing countries, women with bleeding disorders lose their marital status or are abandoned by their spouses due to the interference of bleeding with their sexual life. Bleeding disorders in women can also have serious consequences for a woman's children and family. Women are often the primary

Table 2: Therapeutic options for women with inherited bleeding disorders in pregnancy

Bleeding disorder	Preferred therapeutic option	Other options
VWD	DDAVP or VWF-containing concentrates	Platelet (type 2B)*
Carriers of hemophilia A	DDAVP or rFVIII	FVIII concentrate
Carriers of hemophilia B	rFIX	FIX concentrate
Fibrinogen abnormalities	Fibrinogen concentrate	SD plasma
FII deficiency	PCC	SD plasma
FV deficiency	SD plasma	n/a
FV + FVIII deficiency	SD plasma or rFVIII	FVIII concentrate
FVII deficiency	rFVIIa	FVII concentrate
FX deficiency	PCC	SD plasma
FXI deficiency	FXI concentrates, rFVIIa, or tranexamic acid	SD plasma
FXIII deficiency	FXIII concentrates	SD plasma
VKCFD	Vitamin K	SD plasma or PCC

F: factor; r: recombinant; SD plasma: fresh frozen plasma virally inactivated using a solvent detergent technique; PCC: prothrombin complex concentrates; VKCFD: hereditary combined deficiency of the vitamin K-dependent clotting factors.

*For patients with severe bleeding in the presence of severe thrombocytopenia (< 20,000 μ L) and who do not respond to VWF concentrates.

caregivers, and their health impacts the nutrition and wellbeing of their children.

Postpartum hemorrhage remains the main cause of maternal death and long-term disability for women around the world. PPH can be prevented or its severity can be moderated by educating women and their birth attendants and by using simple measures to prevent uterine atony that can be adopted even in rural settings. Identifying young girls and women with heavy menstrual bleeding and managing their menstruation and iron deficiency are crucial in improving women's health in general.

The benefits of spacing pregnancies and limiting births are well known. Every effort should be made for provision of family planning services for all women. As discussed above, LNG-IUS is a reliable contraceptive for up to five to eight years. It also reduces menstrual bleeding and therefore prevents iron deficiency, which is a great threat to women's health, especially in developing countries.

Recently, several advocacy programs (such as Women Bleed Too in the U.K., Project Red Flag in the U.S.A.,

and the women's program of the Canadian Hemophilia Society) have been created to raise awareness about women with bleeding disorders and to improve their quality of care and life. These efforts no doubt have been crucial in increasing the number of women diagnosed with these disorders who can then be appropriately referred to and managed at hemophilia treatment centres in western countries. However, for the majority of women in the world, a bleeding disorder remains a hidden disease to be suffered silently. Joint efforts among women's advocacy groups, interested professionals, and organizations ensure continued progress. International collaboration and sharing strategies across countries and cultures will help extend the benefits to women around the world.

Useful websites

www.wfh.org

www.womenbleedtoo.org.uk

www.haemophilia.org.uk

www.hemophilia.org

www.projectredflag.org

www.hemophilia.ca

www.haemophilia.org.nz

www.womenshealth.about.com



References

1. Roberts HR, Escobar MA. Other clotting factor deficiencies. In: Hoffman R, editor. Hematology: Basic Principles and Practice, 4th Edition. 3rd ed. NYC: Churchill Livingstone; 2005.
2. Plug I, Mauser-Bunschoten EP, Brocker-Vriends AH, van Amstel HK, van der Bom JG, van Diemen-Homan JE, et al. Bleeding in carriers of hemophilia. *Blood* 2006; 108(1): 52-6.
3. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood* 1987; 69(2): 454-9.
4. Werner EJ, Broxson EH, Tucker EL, Giroux DS, Shults J, Abshire TC. Prevalence of von Willebrand disease in children: a multiethnic study. *J Pediatr* 1993; 123(6): 893-8.
5. ACOG, *Management of anovulatory bleeding*. 2000, American College of Obstetricians and Gynecologists: Washington, DC. p. 1-12.
6. Kadir RA, Economides DL, Sabin CA, Pollard D, Lee CA. Assessment of menstrual blood loss and gynaecological problems in patients with inherited bleeding disorders. *Haemophilia* 1999; 5(1): 40-8.
7. Kouides PA, Phatak PD, Burkart P, Braggins C, Cox C, Bernstein Z, et al. Gynaecological and obstetrical morbidity in women with type I von Willebrand disease: results of a patient survey. *Haemophilia* 2000; 6(6): 643-8.
8. Ragni MV, Bontempo FA, Hassett AC. von Willebrand disease and bleeding in women. *Haemophilia* 1999; 5(5): 313-7.
9. Sramek A, Eikenboom JC, Briet E, Vandenbroucke JP, Rosendaal FR. Usefulness of patient interview in bleeding disorders. *Arch Intern Med* 1995; 155(13): 1409-15.
10. Lopez JA, Andrews RK, fshar-Kharghan V, Berndt MC. Bernard-Soulier syndrome. *Blood* 1998; 91(12): 4397-418.
11. George JN, Caen JP, Nurden AT. Glanzmann's thrombasthenia: the spectrum of clinical disease. *Blood* 1990; 75(7): 1383-95.
12. Kadir RA, Economides DL, Lee CA. Factor XI deficiency in women. *American Journal of Hematology* 1999; 60(1): 48-54.
13. James AH. More than menorrhagia: a review of the obstetric and gynaecological manifestations of bleeding disorders. *Haemophilia* 2005; 11(4): 295-307.
14. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990; 97(8): 734-9.
15. Janssen CA, Scholten PC, Heintz AP. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. *Obstet Gynecol* 1995; 85(6): 977-82.
16. Reid PC, Coker A, Coltart R. Assessment of menstrual blood loss using a pictorial chart: a validation study. *Bjog* 2000; 107(3): 320-2.
17. Kingman CE, Kadir RA, Lee CA, Economides DL. The use of levonorgestrel-releasing intrauterine system for treatment of menorrhagia in women with inherited bleeding disorders. *Bjog* 2004; 111(12): 1425-8.
18. Kouides PA, Heit JA, Philipp CS, Stein SF, Lukes AS, Byams VR, et al. A multi-site, prospective cross-over study of intranasal desmopressin and oral tranexamic acid in women with menorrhagia and abnormal laboratory hemostasis. *Blood* 2007; 110 (ASH Annual Meeting Abstracts): 711.
19. Warner PE, Critchley HO, Lumsden MA, Campbell-Brown M, Douglas A, Murray GD. Menorrhagia I: measured blood loss, clinical features, and outcome in women with heavy periods: a survey with follow-up data. *American Journal of Obstetrics and Gynecology* 2004; 190(5): 1216-23.
20. Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA. von Willebrand disease in women with menorrhagia: a systematic review. *Bjog* 2004; 111(7): 734-40.
21. Philipp CS, Dilley A, Miller CH, Evatt B, Baranwal A, Schwartz R et al. Platelet functional defects in women with unexplained menorrhagia. *J Thromb Haemost* 2003; 1(3): 477-84.
22. Lee CA, Chi C, Pavord SR, Bolton-Maggs PH, Pollard D, Hinchcliffe-Wood A et al. The obstetric and gynaecological management of women with inherited bleeding disorders—review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2006; 12(4): 301-36.

23. Kirtava A, Drews C, Lally C, Dilley A, Evatt B. Medical, reproductive and psychosocial experiences of women diagnosed with von Willebrand's disease receiving care in haemophilia treatment centres: a case-control study. *Haemophilia* 2003; 9(3): 292-7.
24. Chuong CJ, Brenner PF. Management of abnormal uterine bleeding. *Am J Obstet Gynecol* 1996; 175(3 Pt 2): 787-92.
25. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J Clin Pharmacol* 1995; 35(3): 209-19.
26. Siegel JE, Kouides PA. Menorrhagia from a haematologist's point of view. Part II: management. *Haemophilia* 2002; 8(3): 339-47.
27. National Institute for Health and Clinical Excellence. Heavy menstrual bleeding. Developed by the National Collaborating Centre for Women's and Children's Health; 2007; NICE clinical guideline 44.
28. Kouides P, Phatak P, Sham RL, Braggins C, Andrew C, Howard F. The efficacy and safety of the levonorgestrel intrauterine device (Mirena) for bleeding disorder-related menorrhagia in an American cohort (abstract). *Haemophilia* 2006; 12 (suppl. 2): 144-147.
29. Ronnerdag M, Odland V. Health effects of long-term use of the intrauterine levonorgestrel-releasing system: A follow-up study over 12 years of continuous use. *Acta Obstet Gynecol Scand* 1999; 78(8):716-21.
30. Sivin I, Stern J, Coutinho E, Mattos CE, el Mahgoub S, Diaz S et al. Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNg 20) and the Copper T380 Ag IUDs. *Contraception* 1991; 44(5): 473-80.
31. Edelman AB, Gallo MF, Jensen JT, Nichols MD, Schulz KF, Grimes DA. Continuous or extended cycle vs. cyclic use of combined oral contraceptives for contraception. *Cochrane Database of Systematic Reviews* 2005; 20(3): CD004695.
32. Maresh MJ, Metcalfe MA, McPherson K, Overton C, Hall V, Hargreaves J et al. The VALUE national hysterectomy study: description of the patients and their surgery. *Bjog* 2002; 109(3): 302-12.
33. Spilsbury K, Hammond I, Bulsara M, Semmens JB. Morbidity outcomes of 78,577 hysterectomies for benign reasons over 23 years. *Bjog* 2008; 115(12): 1473-83.
34. El-Nashar SA, Hopkins MR, Feitoza SS, Pruthi RK, Barnes SA, Gebhart JB, Cliby WA, Famuyide AO. Global endometrial ablation for menorrhagia in women with bleeding disorders. *Obstet Gynecol* 2007; 109(6): 1381-7.
35. Lethaby A, Hickey M, Garry R. Endometrial destruction techniques for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2005; 19(4): CD001501.
36. Ozelo MC, Svirin P, Larina L. Use of recombinant factor VIIa in the management of severe bleeding episodes in patients with Bernard-Soulier syndrome. *Annals of Hematology* 2005; 84(12): 816-22.
37. DeVore GR, Owens O, Kase N. Use of intravenous Premarin in the treatment of dysfunctional uterine bleeding—a double-blind randomized control study. *Obstetrics and Gynecology* 1982; 59(3): 285-91.
38. Amsterdam A, Jakubowski A, Castro-Malaspina H, Baxi E, Kauff N, Krychman M et al. Treatment of menorrhagia in women undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplantation* 2004; 34(4): 363-6.
39. Laufer MR, Townsend NL, Parsons KE, Brody KA, Diller LR, Emans SJ et al. Inducing amenorrhea during bone marrow transplantation: A pilot study of leuprolide acetate. *Journal of Reproductive Medicine* 1997; 42(9): 537-41.
40. Rouhani G, Menon S, Burgis J, Bacon J. An unusual method to manage a rare blood dyscrasia. *J Pediatr Adolesc Gynecol* 2003; 20(2): S123 - S124.
41. Markovitch O, Ellis M, Holzinger M, Goldberger S, Beyth Y. Severe juvenile vaginal bleeding due to Glanzmann's thrombasthenia: case report and review of the literature. *Am J Hematol* 1998; 57(3): 225-7.
42. Bowkley CW, Dubel GJ, Haas RA, Soares GM, Ahn SH. Uterine artery embolization for control of life-threatening hemorrhage at menarche: brief report. *J Vasc Interv Radiol* 2007; 18(1 Pt 1): 127-31.

43. Nichols WL, Hultin MB, James AH, Manco-Johnson MJ, Montgomery RR, Ortel TL et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia* 2008; 14(2): 171-232.
44. Michaelides K, Tuddenham EG, Turner C, Lavender B, Lavery SA. Live birth following the first mutation specific pre-implantation genetic diagnosis for haemophilia A. *Thromb Haemost* 2006; 95: 373-379.
45. Bremme KA. Haemostatic changes in pregnancy. *Best Pract Res Clin Haematol* 2003; 16(2): 153-68.
46. Chi C, Kadir RA. Obstetric management. In: Lee CA, Kadir RA, Kouides PA, editors. *Inherited bleeding disorders in women*. Wiley-Blackwell; 2009. p. 124-0.
47. Bolton-Maggs PH, Perry DJ, Chalmers EA, Parapia LA, Wilde JT, Williams MD et al. The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. *Haemophilia* 2004; 10(5): 593-628.
48. Lee CA, Chi C, Pavord SR, Bolton-Maggs PH, Pollard D, Hinchcliffe-Wood A et al. The obstetric and gynaecological management of women with inherited bleeding disorders – review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2006; 12(4): 301-36.
49. Ljung R, Lindgren AC, Petrini P, Tengborn L. Normal vaginal delivery is to be recommended for haemophilia carrier gravidae. *Acta Paediatr* 1994; 83(6): 609-11.
50. Chi C, Lee CA, Shiltagh N, Khan A, Pollard D, Kadir RA. Pregnancy in carriers of haemophilia. *Haemophilia* 2008; 14(1): 56-64.
51. American College of Obstetricians and Gynecologists, Postpartum Hemorrhage Practice Bulletin No. 76. 2006, p. 1-9.
52. Gardella C, Taylor M, Benedetti T, Hitti J, Critchlow C. The effect of sequential use of vacuum and forceps for assisted vaginal delivery on neonatal and maternal outcomes. *Am J Obstet Gynecol* 2001; 185(4): 896-902.
53. United Kingdom Haemophilia Centre Doctors' Organisation. Guidelines on the selection and use of haemostatic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia* 2003; 9(1): 1-23.
54. Greer IA, Lowe GD, Walker JJ, Forbes CD. Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. *Br J Obstet Gynaecol* 1991; 98(9): 909-18.
55. Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL. Pregnancy in women with von Willebrand's disease or factor XI deficiency. *Br J Obstet Gynaecol* 1998; 105(3): 314-21.
56. Shankar M, Chi C, Kadir RA. Review of quality of life: menorrhagia in women with or without inherited bleeding disorders. *Haemophilia* 2008; 14(1): 15-20.
57. Barr RD, Sek J, Horsman J, Furlong W, Saleh M, Pai M et al. Health status and health-related quality of life associated with von Willebrand disease. *American Journal of Hematology* 2003; 73(2): 108-14.



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