

GUIDELINES

The obstetric and gynaecological management of women with inherited bleeding disorders – review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization

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Summary. The gynaecological and obstetric management of women with inherited coagulation disorders requires close collaboration between obstetrician/gynaecologists and haematologists. Ideally these women should be managed in a joint disciplinary clinic where expertise and facilities are available to provide comprehensive assessment of the bleeding disorder and a combined plan of management. The haematologist should arrange and interpret laborat-

ory tests and make provision for appropriate replacement therapy. These guidelines have been provided for healthcare professionals for information and guidance and it is also intended that they are readily available for women with bleeding disorders.

Keywords: carrier of haemophilia, guidelines, inherited bleeding disorders, UKHCDO, von Willebrand's disease, women

Introduction

Women with inherited bleeding disorders are particularly at risk of bleeding complications from regular haemostatic challenges during menstruation and childbirth. In the last decade, there has been an international research interest in women with inherited bleeding disorders. This has led to considerable progress in the identification of obstetric and gynaecological problems in these women and raising clinical awareness amongst their care providers. Menorrhagia is the commonest bleeding symptoms in women with inherited bleeding disorders and could be the first or only

presenting symptom. Childbirth also presents an intrinsic haemostatic challenge to these women. They require specialized and individualized care during pregnancy. Particular aspects of their obstetric management include preconception counselling, prenatal diagnosis and antenatal, intrapartum and postpartum care. We provide these guidelines based on collective clinical experience and the published literature. It is aimed to provide guidance for healthcare professionals in the management of women with inherited bleeding disorders and is also available as information for the women.

Search strategy

Each section has been written by one or more members of the group who have a particular knowledge of the bleeding disorder or the gynaecological or obstetric management. The medical literature was searched using key words and cross-reference was

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made to already published relevant guidelines in order to achieve conformity. A draft copy of the guideline was sent for consultation to the Royal College of Obstetricians and Gynaecologists, Royal College of Physicians, Royal College of Pathologists, Royal College of Anaesthetists, Royal College of Nursing, Royal College of Midwives, Royal College of Paediatrics and Child Health, British Society for Haematology the Obstetric Haematology Group, World Federation of Haemophilia, The Haemophilia Society, Women Bleed Too, UKHCDO and the National Institute of Clinical Excellence. The responses were noted. Recommendations have been based on reports with the highest levels of evidence (Appendix 1).

Useful websites

- 1 Haemophilia society: <http://www.haemophilia.org.uk>; Women Bleed Too: <http://www.womenbleedtoo.org.uk>.
- 2 Royal College of Obstetricians and Gynaecologists: <http://www.rcog.org.uk>.
- 3 United Kingdom Haemophilia Centre Doctors' Organisation: <http://www.ukhcdo.org>.
- 4 The Cochrane Library: <http://www.cochrane.org>.
- 5 National Institute for Health and Clinical Excellence: <http://www.nice.org.uk>.

Obstetrics

Haemophilia

Genetic counselling and pre-pregnancy care

Inheritance. Haemophilia A and B are sex-linked recessive disorders with an incidence of one in 5000 and one in 30 000 male births respectively. The genes for factor VIII (FVIII) and factor IX (FIX) are located on the X-chromosome. Carriers of haemophilia have a 50% chance of passing on the gene defect to their offspring; in each pregnancy there is a 50% chance of having an affected son and a 50% chance of having a daughter who will also be a carrier of the condition.

As the nature of haemophilia is consistent amongst family members, carriers can be informed whether their risk is for severe, moderate or mild haemophilia. There is also a genetic element to the development of inhibitors which is partly due to the effect of the same mutation, although other genetic factors may be involved [1].

Genetic counselling. In families at risk of having a child with haemophilia, assessment of carrier status and counselling should ideally be carried out before

conception to allow considerations for suitable reproductive options. The aims of counselling are to provide prospective parents with adequate information that enables them to reach a decision that is appropriate to their situation and to provide them with support throughout the process. Counselling should include assessment and discussion of the genetic risk, the options of prenatal testing that are available with the limitations and potential complications, and discussions on the subsequent choices if the fetus is found to be affected. This should be undertaken by a team of appropriate staff from the haemophilia centre, the fetal medicine unit and the clinical genetics team. UKHCDO has produced guidelines on the framework of genetic service provision for haemophilia and other inherited bleeding disorders [2].

Reproductive options. Families known to be at risk of transmitting an inherited bleeding disorder to their children may have the options of: (i) conceiving naturally and having prenatal diagnosis during pregnancy with the option of termination if the fetus is found to be affected; (ii) declining prenatal testing and accepting the risk and consequences of having an affected child; (iii) not having a child; (iv) adopting a child; (v) considering assisted conception techniques using donor egg or sperm as indicated; and (vi) considering preimplantation genetic diagnosis (PGD) with embryo selection. The decision is influenced by ethnic and cultural issues, the severity of haemophilia in the family, and the personal/family experience of the disorder.

Preimplantation diagnosis. PGD uses *in vitro* fertilization (IVF) to create embryos, tests one or two cells from each embryo for the specific genetic abnormality and identifies unaffected embryos for the transfer to the uterus, obviating the need for prenatal diagnosis and birth of an affected child. It is a relatively new technique and currently, evidence of its effectiveness and safety is still limited [3]. In haemophilia, initially PGD only provided diagnosis of fetal sex but there have been reports of specific diagnosis more recently [4]. It is likely to become a realistic option for more couples at risk of having a child affected by haemophilia in the near future. However, IVF is costly, stressful and the success rates (overall live birth rate ~22%) are much lower than spontaneous conception [5]. On current evidence PGD may be indicated in some individual cases after careful counselling and assessment but should not be regarded as a standard service [6]. It is required by the Human Fertilisation and Embryology Authority for all PGD to be carried out in licensed centres. Best practice guidelines for clinical PGD and screening

have been produced by the European Society of Human Reproduction and Embryology PGD Consortium [7].

Pre-pregnancy counselling should be offered to carriers of haemophilia to discuss suitable reproductive options and methods of prenatal diagnosis (grade C, level IV).

Pregnancy in carriers of haemophilia should be managed by a multidisciplinary team including an obstetrician, haematologist and anaesthetist (grade C, level IV).

Prenatal diagnosis. This should be undertaken in centres with full genetic, haematological and obstetric expertise. There are invasive and non-invasive methods available for prenatal diagnosis of haemophilia.

(i) *Invasive methods for specific diagnosis.* Chorionic villus sampling (CVS) is the principal method used for prenatal diagnosis of haemophilia. The procedure is performed at 11–14 weeks of gestation under ultrasound guidance to obtain a sample of chorionic villi for analysis. It is recommended that CVS should not be performed prior to 10 weeks of gestation due to reports of its association with limb defects when carried out before this gestation [8]. It has the advantage over amniocentesis of permitting diagnosis in the first trimester. If termination of pregnancy is opted for, it is possibly less traumatic and acceptable to the patient. Transabdominal CVS carries a similar risk of miscarriage as amniocentesis which is approximately 1–2% [9]. However, each unit should audit the outcomes of invasive procedures performed and advise patients of the respective complication rates.

Currently fetal sex cannot be determined with 100% accuracy in the first trimester by ultrasound, which means female fetuses cannot be excluded and are exposed to the risk. Amniocentesis, which can also be used for prenatal diagnosis, allows exclusion of female fetuses identified by ultrasound, but is performed later than CVS (after 15 weeks of gestation). This procedure is also performed under ultrasound guidance to obtain a sample of amniotic fluid for cell karyotyping and source of DNA. The rate of miscarriage associated with amniocentesis is approximately 1% [10].

Cordocentesis, ultrasound guided fetal blood sampling, was previously performed to obtain fetal blood for clotting factor assay. However, it is very rarely performed today. It should only be considered if all other possible techniques cannot be used or do not give conclusive results. This option may be

considered if a woman wishes to ensure that she does not have a child affected with severe haemophilia and the causative mutation cannot be identified. The procedure is reported to have a 1.25% risk of procedure-related fetal loss when performed for non-chromosomal indications and by an experienced operator [11]. This risk is possibly higher if the fetus is affected with haemophilia due to the risk of cord bleeding. The levels of FVIII and FIX in a normal fetus at 19 weeks gestation are approximately 40 and 10 IU dL⁻¹, respectively [12,13], which are significantly lower than in an adult. It is therefore important to ensure no maternal blood contamination in the sample by checking the mean corpuscular volume (MCV) of the erythrocytes (>120 fL for fetal MCV and ~ 90 fL for maternal MCV) or by the Kleihauer technique showing resistance of fetal haemoglobin to acid elution.

Prophylaxis for invasive testing. As these procedures are carried out early in pregnancy, the FVIII level is unlikely to have risen significantly. Therefore it is essential to check the mother's clotting factor level (FVIII or FIX) and arrange prophylactic treatment for any invasive prenatal diagnostic test if the level is <50 IU dL⁻¹. All invasive testing may cause fetomaternal haemorrhage; therefore, anti-D immunoglobulin should be given to Rhesus D-negative mothers.

Chorionic villus sampling is the method of choice for specific prenatal diagnosis of haemophilia. Maternal clotting factor level should be checked prior to any invasive procedures and prophylactic treatment arranged if the level is <50 IU dL⁻¹ (grade C, level IV).

Detailed guidelines on amniocentesis and CVS [14] and on the provision of clinical and laboratory genetic services for haemophilia [2] are available.

(ii) *Non-invasive methods for determination of fetal sex.* Non-invasive methods are at present limited to fetal gender determination. Knowledge of fetal sex is beneficial in pregnancies at risk of haemophilia. Its importance should be emphasized to couples who do not wish to have prenatal diagnosis. If the fetus is identified as female, the mother can be reassured especially when specific mutational diagnosis is not possible or when the mother is unsure of her feelings towards termination of pregnancy. The parents will then have the option of avoiding invasive testing in these cases. Knowledge of fetal sex is also helpful for labour management as invasive monitoring techniques, vacuum extraction and difficult forceps deliveries

should be avoided when the coagulation status of the male fetus is unknown in order to minimize the risk of haemorrhagic complications. If the parents do not wish to know the sex of the baby, this information should be made available to the midwives and obstetricians caring for the women in labour.

Ultrasound assessment in the second and third trimesters can accurately determine fetal sex [15–19]. Improvements in the resolution of ultrasound equipments have now provided the possibility of detailed visualization of the fetus in early pregnancy. The morphological aspect of the external genitalia is identical in both sexes until 11 weeks of gestation, but after this stage, there is rapid differentiation of the genitalia [20]. The direction at which the fetal phallus points in the mid-sagittal plan is different between male (caudally) and female (anteriorly). These findings have been utilized by several groups to assess fetal gender from 11 weeks of gestation [21,22]. The sensitivity of this technique, however, is limited especially at 11–12 weeks of gestation. In the study by Whitlow *et al.* [21], the overall success of correctly assigning fetal gender increased with gestational age from 46% to 75%, 79% and 90% at 11, 12, 13 and 14 weeks respectively. In the study by Efrat *et al.* [22], the accuracy of sex determination also increased with gestation from 70.3% to 98.7% and 100% at 11, 12 and 13 weeks respectively. The sensitivity of fetal gender determination in the first trimester is limited by two factors. First, visualization of the genital tubercle is not always possible at such early gestations. Secondly, differentiation of the genital tubercle into the male or female phallus only begins at 11 weeks of gestation, so this sign cannot be used prior to this stage. Due to these limitations, this technique has not been introduced into routine practice and is currently only performed in specialized centres.

An alternative non-invasive method of determining fetal sex is by assessing free fetal DNA in the maternal circulation for the presence or the absence of Y-chromosome-specific DNA sequence. Technical advances, such as the development of quantitative real-time polymerase chain reaction, have allowed several groups to demonstrate a 100% sensitivity and specificity in the detection of male fetuses [23–25]. Free fetal DNA has been detected as early as the fifth week of pregnancy [24], but concentrations, and subsequently the sensitivity of the test, increase with advancing gestation. There is the potential to determine fetal sex using this technique prior to 11 weeks, the earliest gestation at which CVS would be performed, hence avoiding invasive testing in female fetuses. This technique, however, is at present still

being performed in research settings. The combined use of two independent non-invasive techniques, ultrasound and analysis of free fetal DNA in maternal blood, as method of assessing fetal sex to increase confidence in the reliability of these tests has been proposed recently [26].

Knowledge of fetal gender allows invasive testing to be avoided in female pregnancies and enables appropriate management of labour and delivery; therefore, the importance of establishing fetal sex in pregnancies at risk of haemophilia should be conveyed to the parents (grade C, level IV).

Management plan. The patient's choice and the results of prenatal testing should be clearly documented in the case note alongside the management plan for pregnancy, labour and delivery. A multidisciplinary team of obstetricians, haematologists, nurse specialists and anaesthetists should be involved in the formulation of this plan.

Antenatal management. Factor VIII levels have been shown to increase significantly in carriers of haemophilia A during pregnancy. Although the majority of patients will develop levels within the normal range, the rise is variable, and a small proportion may still have low levels at term [27,28]. In contrast, FIX levels do not rise significantly in carriers of haemophilia B [28].

The risk of bleeding in early pregnancy and miscarriage is unknown in carriers of haemophilia, but there is evidence that the risk of antepartum haemorrhage (bleeding from the genital tract after the 22nd week of pregnancy) is not increased [27,28].

Women may be exposed to various haemostatic challenges during pregnancy such as invasive prenatal diagnostic tests, termination of pregnancy and spontaneous miscarriage. All of these may be complicated by excessive and prolonged bleeding.

Factors VIII and IX levels should be checked at booking, and at 28 and 34 weeks of gestation, especially in those with low pre-pregnancy levels (<50 IU dL⁻¹). Monitoring in the third trimester is essential in order to plan the management of labour and the provision of prophylactic treatment to minimize the risk of postpartum haemorrhage (PPH).

Carriers of haemophilia should have their clotting factor level (FVIII or FIX) checked at booking and at 28 and 34 weeks of gestation to allow appropriate management of labour and delivery and to assess the need for prophylactic treatment (grade C, level IV).

Treatment Due to the significant rise of FVIII level during pregnancy, treatment with coagulation factor concentrate is rarely required during pregnancy in carriers of haemophilia A [28]. On the contrary, carriers of haemophilia B with a low baseline level are more likely to require haemostatic support to cover delivery, especially if Caesarean section is required as FIX level does not rise significantly in pregnancy.

If treatment is required in carriers of either haemophilia A or B, recombinant products should be regarded as the products of choice [29]. Plasma-derived clotting factor concentrates, treated with the currently available virucidal method have no risk of transmitting the hepatitis B and C virus and human immunodeficiency virus [30]. However, they have the potential to transmit hepatitis A and parvovirus B19 [31,32]. While not normally a serious infection in non-immunocompromised adults, parvovirus infection of the fetus may result in hydrops fetalis and fetal death.

Desmopressin [1-desamino-8-D-arginine vasopressin (DDAVP)] increases plasma levels of von Willebrand factor (VWF) and FVIII in the blood and thus has potential use in carriers of haemophilia A. It has no effect on FIX levels, hence is of no value in carriers of haemophilia B. The use of DDAVP during pregnancy is controversial because of the potential risks of placental insufficiency due to arterial vasoconstriction and of miscarriage or preterm labour due to an oxytocic effect [33]. However, in contrast to naturally occurring vasopressin, DDAVP has minimal vasoconstrictive and oxytocic effects, consistent with its predominant V2 vasopressin receptor activity. There is a risk of maternal and/or neonatal hyponatraemia as a result of DDAVP's more potent and prolonged antidiuretic effect, compared with that of natural hormone vasopressin [33]. Therefore, restriction of fluid intake is required to accompany its use. The efficacy and safety of DDAVP for prophylaxis or treatment of pregnancy-associated bleeding have not been systematically studied, but evidence of its safety during pregnancy in women with diabetes insipidus using smaller doses is available [34]. In a series of 27 haemophilia A carriers with low FVIII levels who received DDAVP for coverage of invasive prenatal diagnostic procedures, there was no serious side effect other than mild facial flushing and headache [35]. DDAVP does not pass into breast milk in significant amounts. Hence, DDAVP may be used in labour and during the postpartum period.

Recombinant FVIII and FIX should be used as the treatment of choice in pregnant carriers of haemophilia A and B (grade C, level IV).

Intrapartum management. Labour and delivery are critical times for carriers of haemophilia and their affected child when they are exposed to various haemostatic challenges. Pregnancies in carriers of haemophilia should be managed in collaboration with a haemophilia centre and arrangement for delivery should be made in advance. It is recommended for women carrying an affected fetus to delivery at a unit where the necessary expertise in the management of this disorder and resources for laboratory testing and clotting factor treatments are readily available.

A delivery plan should be made in advance and for women carrying an affected fetus, delivery should be planned at a unit where the necessary expertise in the management of this disorder and resources for laboratory testing and clotting factor treatments are readily available (grade C, level IV).

Labour. During labour, the maternal coagulation screen and appropriate factor assays should be checked, as well as saving serum for cross-matching. If it is difficult to access factor levels in labour, it is acceptable to rely on the third trimester levels to formulate a plan. When the factor level is $<50 \text{ IU dL}^{-1}$, an intravenous line should be established and prophylactic treatment given for labour and the postpartum period.

Spontaneous labour should be allowed where possible and special consideration should be given when labour is to be induced. Induced labour is likely to be prolonged and associated with the need for instrumental delivery or emergency caesarean section particularly in primigravida women with unfavourable cervix at the start of induction. In these cases, a multidisciplinary team of obstetrician and haematologist along with the mother should perform a careful risk assessment. In some circumstances, elective caesarean section could be considered less traumatic to both the mother and her affected son.

Regional analgesia and anaesthesia. A plan of management should be devised with the anaesthetist prior to labour/delivery and discussed with the patient. The use of regional block in patients with bleeding disorders is controversial because of the potential risk of epidural or spinal haemorrhage and haematoma, which may lead to permanent neurological damage. However, provided the coagulation screen is normal and the relevant factor level is above 50 IU dL^{-1} , regional block is not contraindicated

[28,36]. In situations where factor levels cannot be assessed due to advanced labour, provided the factor level is $>50 \text{ IU dL}^{-1}$ in the third trimester, it is then sufficient to assess the platelet count, partial thromboplastin time (PTT) and prothrombin time (PT). Regional block in carriers of haemophilia should be performed by an expert anaesthetist with the help of a specialized haematologist for assessment of coagulation status and arrangement of treatment when needed. The epidural should be placed in the midline, which decreases the chance of intravascular puncture with the epidural catheter [37], and the lowest concentration of a local anaesthetic and narcotic mixture should be used to achieve analgesia so as to maintain motor function [38]. The extent of motor block should be assessed frequently until the anaesthetic has worn off and the catheter removed. If the degree of motor block is more than that expected or if the anaesthetic appears to be prolonged, magnetic resonance imaging should be arranged to check for development of an epidural haematoma. It is important to check factor levels prior to the removal of epidural catheter as the pregnancy-induced rise in factor levels may quickly reverse after birth and bleeding in the spinal canal may then arise. Intramuscular analgesia and non-steroidal anti-inflammatory drugs (NSAID) should be avoided if factor levels are below normal.

Regional block in carriers of haemophilia is not contraindicated if the coagulation screen is normal and the relevant factor level is above 50 IU dL^{-1} (or raised to $>50 \text{ IU dL}^{-1}$ by prophylactic treatment). It should be performed by an expert anaesthetist with the help of a specialized haematologist for assessment of coagulation status and arrangement of treatment if required (grade C, level IV).

Fetal monitoring. The use of fetal scalp electrodes and fetal blood sampling should be avoided in affected male fetuses or when fetal sex or coagulation status of male fetus is unknown. Although no bleeding complication in affected fetuses and neonates has been reported so far from these procedures, it is advisable to avoid their use due to the potential risk of scalp haemorrhage in affected male fetuses.

The use of fetal scalp electrodes and fetal blood sampling should be avoided in affected male fetuses or when fetal sex or coagulation status of male fetus is unknown (group C, level IV).

Delivery. Affected fetuses are at risk of serious head bleeding, including cephalohaematoma and intracranial haemorrhage (ICH), from the process

of birth. The safest method of delivery for fetuses at risk is controversial. In a survey in the USA, 11% of obstetricians preferred to deliver pregnant carriers of haemophilia by caesarean section [39]. Ljung *et al.* [40] reviewed 117 children with moderate to severe haemophilia born between 1970 and 1990 and found 23 neonatal bleedings associated with delivery. The risk of haemorrhage was 10% with vaginal delivery, 64% with vacuum extraction and 23% with caesarean section. The risk of head bleeding specifically was 3% with vaginal delivery, 64% with vacuum extraction and 15% with caesarean section. It was concluded that the risk of serious bleeding during normal vaginal delivery is small and that delivery of all fetuses at risk of haemophilia by caesarean section is not expected to eliminate this risk. However, the use of vacuum extraction or forceps, or prolonged labour especially prolonged second stage of labour, should be avoided as they are associated with an increased risk of cephalohaematoma or intracranial bleeding [28,40].

In principle, fetuses at risk of haemophilia should be delivered by the least traumatic method and early recourse to caesarean section should be considered. Although vacuum extraction should not be used, low forceps delivery may be considered less traumatic than caesarean section when the head is deeply engaged in the pelvis and it is expected to be an easy outlet procedure. In these cases, the procedure should be performed by an experienced obstetrician. Care should be taken in minimizing maternal genital and perineal trauma in order to reduce the risk of PPH.

Vacuum extraction, mid-cavity forceps and prolonged labour should be avoided in affected male fetuses or when fetal sex or coagulation status of male fetus is unknown. Delivery should be achieved by the least traumatic method and early recourse to caesarean section should be considered (grade C, level IV).

Postpartum management. The pregnancy-induced rise in clotting factors (FVIII and VWF, not FIX) falls rapidly after delivery. Carriers of haemophilia are at increased risk of both primary (defined as $>500 \text{ ml}$ blood loss in the first 24 h) and secondary (after the first 24 h) PPH. The incidences of primary and secondary PPH in the general population are approximately 5–8% and 0.8%, respectively [41,42]. In a study amongst haemophilia carriers the incidence of primary and secondary PPH were increased at 22% and 11%, respectively [28].

Another study reported a significantly higher incidence of prolonged bleeding after delivery among haemophilia carriers (22%) in comparison with the control group (6%) [43]. Five PPHs and a large perineal haematoma were reported among 43 pregnancies in haemophilia carriers [27]. It seems that FVIII or FIX activity has a significant influence on the risk of bleeding in haemophilia carriers [28,43]. The factor level should ideally be checked daily after delivery. It should be maintained above 50 IU dL⁻¹ for at least 3 days, or 5 days if caesarean section has been performed, in order to minimize the risk of primary and secondary PPH. The risk of PPH can be further reduced by active management of the third stage of labour [44] and minimizing maternal genital and perineal trauma.

Active management of third stage should be practised in carriers of haemophilia (grade C, level IV).

In the event of PPH, after correction of hypovolaemia, factor replacement therapy or treatment with DDAVP should be instituted in close collaboration with the local haemophilia centre. Obstetric causes for excessive bleeding should not be overlooked. Consideration should be given to tranexamic acid to reduce bleeding in cases of heavy lochia.

Factor levels should be monitored postdelivery and maintained above 50 IU dL⁻¹ for at least 3 days, or 5 days if caesarean section has been performed (grade C, level IV).

Neonates. Neonates affected with haemophilia may be at risk of bleeding at puncture sites, from surgical interventions (circumcision being the commonest), and spontaneous bleeding such as bruising, organ and joint bleeding. If necessary, heel pricks should be carried out carefully with pressure applied to the site for a full 5 min afterwards. Any prolonged bleeding or excessive bruising at the site of the heel prick should be reported to the haemophilia team immediately.

Intramuscular injections and venepunctures should be avoided in neonates affected with haemophilia or whose coagulation status is unknown. Vitamin K should be given orally and routine immunizations should be given intradermally or subcutaneously. Circumcision should be delayed until the coagulation status of the neonate is known and appropriate management can be arranged by the haematologist (grade C, level IV).

Cord blood sample. After delivery, a cord blood sample should be obtained in a citrated tube and

transferred to coagulation laboratory for coagulation factor assay within two hours. The result should be conveyed to the parents by an appropriate member of the haemophilia team, usually one of the staff of the haemophilia centre. Early diagnosis allows for prevention of bleeds and appropriate management of suspected or documented bleeds.

Cord blood should be collected from all male offspring of carriers of haemophilia to assess clotting factor levels for identification and early management of newborns at risk. The results of the tests should be conveyed to the parents by an appropriate member of the haemophilia team (grade C, level IV).

Intracranial haemorrhage. The incidence of ICH in neonates with haemophilia has been estimated at 1–4% and these events are typically associated with significant morbidity and mortality [45]. A review of bleeding episodes in 349 newborns with haemophilia in 66 publications found 366 bleeding episodes; head bleeding being the most common with intracranial bleeding and subgaleal/cephalohaematomas accounting for 27% and 13% of all bleeding episodes [46]. It is debated as to whether all haemophilic infants should have a routine cranial ultrasound. A normal scan does not exclude all bleeds. It is recognized that cranial ultrasound is a relatively poor investigation for the detection of subdural haemorrhage, which is the commonest site of ICH in the neonates. In addition, the optimal time of scanning is unclear reflecting the typically delayed presentation of intracranial bleeding. A survey of haemophilia centres in the UK showed that only 41% of respondents would routinely perform cranial ultrasound on neonates with severe haemophilia and 21% would perform ultrasound in the presence of clinical signs suggestive of bleeding [47]. No evidence currently exists to support the routine use of cranial ultrasound. However, it is recommended that if labour has been traumatic, e.g. following forceps delivery or prolonged labour, preterm or there are any clinical signs suggestive of bleeding, a cranial ultrasound scan should be performed.

Community midwives should be informed of affected babies. They and the mothers should be made aware of the early signs of ICH (e.g. lethargy, vomiting, seizures and poor feeding) as the reported mean age at which the haemorrhage occurred is 4.5 days (range, birth to 1 month) [45] when both the mother and baby are usually discharged home.

The administration of routine prophylaxis postdelivery is controversial. It has been argued by those in favour of early prophylaxis that it is illogical to

manage potential cranial trauma in neonates expectantly [48]. However, recently, there have been reports of an increased risk of inhibitor development when clotting factor is administered in the early neonatal period [49,50]. This association remains to be clarified by larger studies as these studies did not specifically address those children treated during the first few days of life and did not take into account other potential risk factors for inhibitor development. Nevertheless, it is advisable to consider prophylaxis in traumatic or premature deliveries and if there is any suspicion of bleeding.

Cranial ultrasound/computed tomography (CT) scans should be arranged for all neonates with haemophilia if labour had been premature, traumatic, e.g. following forceps delivery or prolonged labour, or if there are any clinical signs suggestive of bleeding. In these cases it is recommended that recombinant clotting factor should be administered to raise the plasma clotting factor to 100 IU dL⁻¹ (grade C, level IV).

von Willebrand's disease

Pre-pregnancy counselling and prenatal diagnosis. von Willebrand's disease is the commonest inherited bleeding disorder with a prevalence of approximately 1% in the general population [51]. It is generally inherited as an autosomal condition, and thus children of either sex may inherit the condition. There are three main types of VWD. Type 1 is the commonest accounting for ~ 70% of all cases. Types 1 and 2 are transmitted as an autosomal dominant trait. The risk of a woman with type 1 VWD transmitting the disease to her child is 50%. However, only 33% of children born to these women are clinically affected, probably because of variable penetrance and expression of the abnormal gene [52]. The same is true for type 2A and most cases of type 2B. However, the situation is more complicated for the other subtypes of type 2 VWD. Extensive family studies are required to assess this risk. Type 3 VWD is an autosomal recessive disorder, and affected individuals are either homozygotes or compound heterozygotes. If a child with type 3 has already been born in the family, the risk of a subsequent child being affected is 25%.

Preconceptual counselling should include the option of prenatal diagnosis. Antenatal diagnosis is not usually required or requested in types 1 and 2 VWD as the bleeding tendency is relatively mild. However, if the fetus is at risk of type 3 (severe) VWD, the parents may wish to consider antenatal diagnosis.

This should be planned in advance to allow the causative mutation(s) or informative polymorphisms to be identified using one of the invasive methods of prenatal diagnosis described above.

The option of prenatal diagnosis should be discussed and offered to women with VWD whose genetic mutation is identifiable, particularly to those at risk of having a child with type 3 VWD (grade C, level IV).

Antenatal management. Haemostatic response to pregnancy is variable in different types and subtypes of VWD. In type I VWD there is usually a progressive increase in FVIII coagulant activity (FVIII:C), VWF antigen (VWF:Ag) and VWF activity (VWF:AC), and correction of the bleeding time (BT) during pregnancy [27,53–55]. Most women with type 1 VWD achieve VWF levels in the normal (non-pregnant) range by the third trimester [56]. Failure of primary haemostasis to improve significantly in pregnancy, especially in severely affected type I women, has been reported [57,58]. In a series of 24 pregnancies in 13 women studied retrospectively, it was noted that FVIII:C and VWF:Ag rose above baseline values by a factor of at least 1.5 during pregnancy in most cases [58]. However, a baseline VWF:AC of <15 IU dL⁻¹ (4/14 cases) was predictive of a third trimester level of <50 IU dL⁻¹ and less marked improvements in VWF:AC [58].

In type 2 VWD, FVIII and VWF antigen levels often increase during pregnancy, but most studies show minimal or no increase in VWF activity levels, and a persistently abnormal pattern of multimers, reflecting the increased production of abnormal VWF [27,56,58]. Despite increased FVIII and VWF production during pregnancy, FVIII:C levels are often low in women with subtype 2N VWD because of impaired binding by the abnormal VWF [59]. In subtype 2B VWD thrombocytopenia may develop or worsen during pregnancy due to increased production of the abnormal intermediate VWF multimers, which bind to platelets and induce spontaneous platelet aggregation [60].

Women with type 3 VWD show little or no increase in their FVIII and VWF plasma levels [54,61].

Due to the great variability of haemostatic response of VWD to pregnancy, regular monitoring of VWF:Ag and VWF:AC together with FVIII:C is essential. This should be performed at presentation, prior to any invasive procedures, and in the third trimester. The platelet count should also be monitored in women with type 2B VWD [60]. If VWF:AC

is <50 IU dL⁻¹, consideration should be made for prophylactic treatment with a clotting factor concentrate containing VWF to cover any invasive procedures and delivery.

A review of 84 pregnancies from 1980 to 1996 of women with all types of VWD showed that 33% (28) reported vaginal bleeding in the first trimester. The overall spontaneous miscarriage rates were 21% in this study [54] and 22% in another study [62]. This is not significantly different from the normal rate of 15% [63]. Even though there appears to be a higher incidence of vaginal bleeding in the first trimester in women with VWD, there is no increase in the miscarriage rate [54,59]. It is likely that these women present more readily if they experience bleeding in early pregnancy. However, there is an increased risk of bleeding complications associated with spontaneous miscarriage or elective termination [54,61,62]. In one study, 10% of spontaneous or elective abortions were complicated by excessive bleeding requiring transfusion. In addition, intermittent bleeding two weeks after miscarriage occurred in 30% of cases [54]. FVIII and VWF do not rise significantly until the second trimester [58] by which stage most miscarriages have already occurred. Therefore, factor levels should be checked in women presenting with spontaneous miscarriages and in those opting for termination of pregnancy. Prophylactic treatment should be given when factor levels are <50 IU dL⁻¹.

Pregnancy in women with VWD should be managed by a multidisciplinary team including an obstetrician, haematologist and anaesthetist (grade C, level IV).

Factor levels including VWF:Ag, VWF:AC and FVIII:C should be checked at booking, 28 and 34 weeks and prior to invasive procedures. Prophylactic treatment should be given when factor levels are <50 IU dL⁻¹ to cover invasive procedures and delivery (grade C, level IV).

Treatment. Desmopressin increases plasma FVIII and VWF levels. However, its use in pregnancy is controversial as discussed previously in its use in carriers of haemophilia. Multiple reports have suggested its effectiveness in the prevention or control of bleeding at the time of abortion and delivery without complications [56,58,64,65]. In one survey, 50% and 34% of haematologists reported using intravenous and intranasal DDAVP, respectively, for PPH in women with type 1 VWD. And only 31% considered pregnancy as a contraindication [66]. DDAVP is not contraindicated in uncompli-

cated pregnancy although like all drugs it should be used with caution. Prolonged administration in pregnancy should be avoided and close monitoring for water retention is important [67]. A fluid restriction of 1 L for 24 h after DDAVP should minimize the risk of fluid overload and consequent hyponatraemia.

Desmopressin can be used in pregnancy, but repeated administration or use in pregnancies complicated with pre-eclampsia must be avoided. Close monitoring for water retention must accompany its use (grade C, level IV).

Virally inactivated concentrate containing VWF is the treatment of choice in women with VWD unresponsive to DDAVP for preventing or controlling pregnancy-associated bleeding.

If FVIII:C or VWF:AC is <50 IU dL⁻¹, prophylactic administration of concentrate containing VWF should be given to minimize maternal haemorrhagic complications [27,54]. Prophylactic infusion should start at the onset of labour, with the aim of raising FVIII:C and VWF:AC to >50 IU dL⁻¹; this should be maintained for at least 3 days after vaginal delivery and at least 5 days after caesarean section [68]. DDAVP can be used in women with type 1 VWD and in some with type 2A, as there is usually a good response to this treatment with no risk of viral transmission. DDAVP should generally be avoided in women with type 2B VWD because it can precipitate thrombocytopenia [69]; platelet transfusions have been given when the platelet count was $<20 \times 10^9$ L in type 2B [60]. Management of type 2N VWD using recombinant FVIII has been reported [70]. Women with type 3 VWD do not respond to DDAVP and as FVIII:C and VWF:AC do not increase in these cases during pregnancy, treatment is required with concentrate containing VWF to cover delivery.

Women with type I VWD generally do not require prophylactic treatment for delivery. In type 2 VWD, treatment is required for operative delivery or if there is perineal trauma. Women with type 3 VWD require treatment for all types of delivery (grade C, level IV).

Tranexamic acid can also be used in the prevention or control of PPH. Although there have not been studies of antifibrinolytic therapy during pregnancy in women with VWD, tranexamic acid has been used to control or prevent bleeding from placental abruption, caesarean section or other obstetric causes without apparent maternal or fetal adverse effect [71–74].

Intrapartum management Management of labour and delivery are similar to that of carriers of haemophilia. It is important to establish both the type and plasma levels of FVIII and VWF so as to plan the management of labour and the provision of prophylactic treatment.

Arrangements for delivery should be made in advance. It is recommended for women with severe VWD to deliver at a unit where the necessary expertise in the management of this disorder and resources for laboratory testing and clotting factor treatments are readily available.

A delivery plan should be made in advance. For women with severe VWD, delivery should be planned at a unit where the necessary expertise in the management of this disorder and resources for laboratory testing and clotting factor treatments are readily available (grade C, level IV).

Epidural anaesthesia. Several case reports have shown women with VWD received epidural anaesthesia without bleeding complications [61,75–77]. In a series, eight women with VWD received regional anaesthesia during labour and delivery without bleeding complications and only one woman received prophylactic therapy as the clotting factor levels were >50 IU dL⁻¹ in the other cases [54]. Epidural anaesthesia may be considered for use in the majority of women with type 1 VWD whose levels have risen to >50 IU dL⁻¹. However, the decision of its use needs to be made jointly by an experienced anaesthetist, obstetrician and haematologist after considerations are given to haemostatic concerns such as the degree of correction of the plasma FVIII:C and VWF levels, possible degree of residual platelet impairment, possible rate of postpartum decline of VWF and the consequent risks of bleeding/spinal haematoma. The risks of an epidural or spinal anaesthetic for caesarean section should be balanced against the risk of a general anaesthetic. In all cases the epidural should be inserted by an experienced anaesthetist. Epidural anaesthesia is generally not recommended for use in type 2 or 3 VWD [67].

Epidural anaesthesia can be offered for use in majority of women with type 1 VWD whose VWF activity is >50 IU dL⁻¹ (or raised to >50 IU dL⁻¹ by prophylactic treatment). It should be carried out by an experienced anaesthetist. It is generally not recommended for use in type 2 or 3 VWD (grade C, level IV).

Delivery. In patients with types 1 and 2 VWD, normal vaginal delivery and Caesarean section are regarded as safe if VWF:AC is >50 IU dL⁻¹ [67].

Treatment with DDAVP or VWF-containing concentrates may be needed. DDAVP is useful in the treatment of type 1 and some type 2 VWD but is of no value in type 3 VWD. In type 3 disease, VWF-containing concentrates are required to cover all types of delivery. Vacuum extraction and mid-cavity/rotational forceps should be avoided, especially in fetuses at risk of having types 2 or 3 VWD, due to the risk of intracranial bleeding. It is recommended that delivery should be achieved by the least traumatic method. Prolonged labour, especially prolonged second stage of labour, should be avoided and early recourse to caesarean section should be considered.

Women with VWF activity <50 IU dL⁻¹ should receive prophylactic treatment at the onset of labour or prior to planned caesarean section (grade C, level IV).

Postpartum management. Postpartum management of women with VWD is similar to that of carriers of haemophilia as they are also at increased risk from primary (>500 ml blood loss in the first 24 h) and secondary (24 h to 6 weeks postpartum) PPH due to the rapid fall in FVIII and VWF levels after delivery. In three series, which included a total of 51 women with information on 92 deliveries, primary PPH complicated 16–29% of pregnancies whilst secondary PPH complicated 20–29% of pregnancies [27,54,58]. The risk of PPH can be reduced by active management of third stage of labour [44] and minimizing maternal genital and perineal trauma.

Active management of third stage should be practised in women with VWD (grade C, level IV).

It is important to check VWF levels postdelivery in women with VWD, particularly those with significantly low pre-pregnancy baseline levels. The risk of PPH appears to be relatively higher in women with types 2 and 3 VWD, especially those with low FVIII and VWF levels (<50 IU dL⁻¹) at term. In these cases it is important to maintain VWF level within the normal range with either DDAVP or VWF-containing concentrates, and for at least 3 days postdelivery, or 5 days if following caesarean section.

There is variable fall in VWF levels to baseline postdelivery. There are anecdotal reports of a decrease from 41 to 9 IU dL⁻¹ over the course of a week [58] and a further case where there was a fall to half values with 24 h postdelivery [55]. On the other hand, the average time of presentation of PPH in women with VWD was found to be 15.7 ± 5.2 days [78]. This implies the potential need for prophylaxis and/or close observation for up to several weeks

postpartum. Prolonged and/or intermittent secondary PPHs have been reported in women with VWD [54,58]. Tranexamic acid or combined oral contraceptive (COC) pills can be used to control postpartum bleeding in these cases. It is recommended that patients are encouraged to report excessive bleeding and haemoglobin levels should be documented.

Factor levels should be monitored postdelivery and prophylaxis given to maintain VWF activity and FVIII levels >50 IU dL⁻¹ for at least 3 days, or 5 days following caesarean section. Tranexamic acid or COC pill should be considered to control prolonged and/or intermittent secondary PPH (grade C, level IV).

Neonates. Neonates with severe VWD are at risk of head bleedings (scalp haematoma and ICH) during labour and delivery. Hence the use of invasive monitoring techniques (fetal scalp electrodes and fetal blood sampling) and instrumental deliveries (vacuum extraction or mid-cavity/rotational forceps) should be avoided in fetuses at risk of having type 2, type 3, or moderately severe type 1 VWD. In neonates affected with mild type I VWD, this risk is very small. In addition, neonates may have some protection from the increase in VWF and FVIII levels induced by the stress of labour [79].

Cord blood sample. After delivery, a cord blood sample should be obtained from newborns at risk of type 3 VWD for assessment. When assessing the neonatal clotting factor levels, it should be appreciated that these correlate with gestational age and reach adult levels at age of 6 months. Thus, although severe forms of these disorders can be diagnosed at the time of birth, mild forms are not always reliably diagnosed due to the increase in VWF and FVIII levels induced by the stress of labour [79]. The child should be screened later during the first year of age. The result should be conveyed to the parents by an appropriate member of staff who is most involved in counselling.

For fetuses at risk of types 2 and 3, or moderately severe type 1 VWD, invasive monitoring techniques, vacuum extraction and rotational/mid-cavity forceps should be avoided and a cord blood sample should be sent for assessment (grade C, level IV).

Intramuscular injections should be avoided until coagulation status is known and vitamin K given orally. Immunization for hepatitis B should be considered and given by intradermal route. Circumcision should also be postponed until the coagulation status is known. If necessary, heel pricks should be

carried out carefully with pressure applied to the site for a full 5 min afterwards. Any prolonged bleeding or excessive bruising at the site of the heel prick should be reported to the haemophilia team immediately.

Intramuscular injections and venepunctures should be avoided in neonates whose coagulation status is unknown. Vitamin K should be given orally and routine immunizations should be given intradermally or subcutaneously. Circumcision should be delayed until the coagulation status of the neonate is known and appropriate management can be arranged by the haematologist (grade C, level IV).

Factor XI deficiency

The inheritance of factor XI (FXI) deficiency is autosomal with severely low levels of <15 IU dL⁻¹ in homozygotes or compound heterozygotes and partial deficiency in heterozygotes, with levels between 15 and 70 IU dL⁻¹ [80,81]. The condition is associated with a much more variable bleeding tendency than haemophilia A or B. Spontaneous bleeding is rare but haemorrhage can occur at sites prone to fibrinolysis and women with partial as well as severe deficiency are at risk of excessive uterine bleeding [82,83]. The bleeding is inconsistent within a family and is also not clearly related to factor levels as in haemophilia A and B [81–84]. Neither does the abnormal genotype causing the condition appear to bear any relationship to bleeding tendency [85]. This unpredictable nature of FXI deficiency makes management for pregnancy and delivery much more difficult and attempts should be made to identify whether the patient has a clinical bleeding tendency and whether other factors are involved, such as coexistence of VWD and platelet malfunction [86].

Pregnancy in women with FXI deficiency requires specialized and individualized care provided collaboratively by an obstetrician, haematologist and anaesthetist (grade C, level IV).

Due to the unpredictability of the condition, attempts should be made to identify the individual's clinical bleeding tendency and the coexistence of confounding factors (grade C, level IV).

Genetic counselling and prenatal diagnosis. Pre-conceptual genetic counselling should be offered to all patients to ascertain whether the mutation is known and discuss the options of prenatal diagnosis. However, due to the large number of different

genetic mutations implicated in FXI deficiency, prenatal diagnosis is often difficult, except in Ashkenazi Jews in whom two different mutations predominate: type II, a stop codon in exon 5 and type III, a missense mutation in exon 9 leading to reduced expression of FXI. Prenatal diagnosis should be offered to patients where there is a risk of severe FXI deficiency.

Prenatal diagnosis should be discussed and offered to patients where there is a risk of severe FXI deficiency (grade C, level IV).

Antenatal management. FXI usually remains constant throughout pregnancy but studies have also shown inconsistencies in levels, with increases or decreases as pregnancy advances [54,87–89]. As it is often not feasible to check levels in an acute situation, routine monitoring should be carried out at booking, 28 and 34 weeks. Invasive procedures such as CVS, amniocentesis and termination of pregnancy can be complicated by excessive or prolonged haemorrhage. Levels should be checked prior to these procedures and prophylaxis with FXI concentrate or, if unavailable, virally inactivated fresh frozen plasma given for patients with severely low levels or a history of bleeding. Probable 'non-bleeders' can be managed expectantly with treatment available on stand-by should bleeding occur.

Factor XI levels should be checked at booking, 28 and 34 weeks and prior to invasive procedures. Many patients can be managed expectantly but patients with severely low levels or a positive bleeding history should be given prophylaxis to cover invasive procedures (grade C, level IV).

Intrapartum management. Patients with FXI levels <15 IU dL⁻¹ have a 16–30% risk of excessive bleeding during delivery [54,85] and should receive prophylactic FXI concentrate or, if unavailable, fresh frozen plasma at the onset of labour or prior to planned induction or caesarean section, unless there is a history of uneventful major surgical procedures without prior treatment. In view of the thrombotic potential of FXI concentrate [90,91], peak levels should not exceed 70 IU dL⁻¹ (normal range 70–150). As for all blood products there are concerns about the risk of transfusion-transmitted infections. Recombinant factor VIIa (rFVIIa) has been used successfully in these patients [92–94], although it is as yet unlicensed in this setting. Its short half-life makes it unsuitable for use to cover labour, but could be used for management of elective caesarean section. The dose used may be lower than the

standard 90 µg kg⁻¹ used in haemophilia patients with inhibitors, but further studies are needed to assess the optimal dose [95].

In patients with levels between 15 and 70 IU dL⁻¹, tranexamic acid should be given if there is a bleeding history or if this is unknown due to the absence of previous haemostatic challenges [96]. Otherwise it is reasonable to keep fresh frozen plasma or FXI concentrate available for patients who develop excessive bleeding [85].

Regional anaesthesia. Epidural anaesthesia has been carried out without complication in FXI-deficient patients [54,97]; however, the consequences of a spinal haematoma with compression of the spinal cord makes it an unacceptable risk and epidural should be avoided in severe cases or women with significant bleeding history. If epidural is necessary, it should be covered with FXI concentrate. FFP contains variable levels of FXI and is not recommended to cover epidural. Recombinant FVIIa may find increased use in the future especially to cover procedures such as caesarean section.

A delivery plan should be made in advance. It is recommended for women with FXI deficiency to deliver at a unit where the necessary expertise in the management of this disorder and resources for laboratory testing and clotting factor treatments are readily available (grade C, level IV).

Women with severe deficiency and/or a bleeding history, should receive prophylactic treatment at the onset of labour or prior to planned induction or caesarean section (grade C, level IV).

Postpartum management. The incidence of primary and secondary PPH has been reported to be 16% and 24%, respectively, in untreated patients with FXI deficiency [54]. Active management of third stage should be practised in women with FXI deficiency. Prophylactic treatment with tranexamic acid should be considered postdelivery. When given, it should be extended for 3 days postpartum or 5 days following caesarean section. The standard dose is 1 g 6–8 hourly. The concomitant use of tranexamic acid and FXI concentrate should be avoided. The half-life of FXI, as determined in 19 patients, was 52 ± 22 h (mean \pm SD) [98], and therefore subsequent doses are seldom needed. Recombinant FVIIa has a half-life of two hours and repeat doses may be required or treatment continued with tranexamic acid. Although the incidence of thrombosis in patients receiving these products is low, attention should be given to simple thromboprophylactic measures including ensurance of adequate hydration and early mobilization.

Active management of third stage should be practised in women with FXI deficiency (grade C, level IV).

Where prophylaxis has been given, it should be extended to 3 days postpartum or 5 days following caesarean section (grade C, level IV).

Neonate. Neonatal haemorrhage due to peripartum events is rare; however, care should be taken to avoid unnecessary trauma to the baby, including avoidance of ventouse extraction, rotational forceps and invasive monitoring techniques.

Spontaneous bleeding or ICH in the neonatal period, have not been reported but a cord blood sample should be taken at birth for FXI level to determine the potential for bleeding during high-risk situations such as circumcision. However, as neonatal levels are reduced to approximately 50% of adult levels, mild FXI deficiency cannot be reliably diagnosed and repeat testing during the first year of life may be indicated.

Intramuscular injections should be avoided, until coagulation status is known, and vitamin K given orally if levels are reduced.

Care should be taken to avoid unnecessary trauma to the baby at delivery and a cord blood sample for FXI level should be obtained (grade C, level IV).

Rare bleeding disorders

The rare coagulation disorders include afibrinogenemia and deficiencies of prothrombin (factor II, FII), factor V (FV), combined V and FVIII, factor VII (FVII), factor X (X) and factor FXIII (FXIII) and have an estimated incidence in the severe form of one in 500 000 (FVII deficiency) to one in 2 million individuals (factor II deficiency) (Table 1). These disorders are inherited as autosomal recessive traits and are generally rarer than haemophilia A and B [99]. However, in racial groups, communities or countries where consanguineous marriages are com-

mon (such as Asian communities and some Muslim countries) they are more common because clinically they are expressed in homozygotes or compound heterozygotes. It is therefore important that doctors and paediatricians are aware of this so that any women or child with a bleeding diathesis is promptly diagnosed and treated.

Genetic counselling and prenatal diagnosis. In general a mutation in the DNA can be identified in the genes encoding the relevant coagulation factors. For each coagulation factor, there are multiple mutations but these are unique for any given family. Thus prevention of rare coagulation disorders through prenatal diagnosis of the underlying mutation is possible for couples who present with an affected child.

Antenatal, intrapartum and postpartum management. The general principles of the management of pregnancy, delivery and the postpartum period in carriers of rare bleeding disorders are similar to those in carriers of haemophilia A and B. However, the available therapies are limited (Table 1) and are plasma derived with the exception of rFVIIa which is recommended for the treatment of FVII deficiency.

The rarity of these disorders and the paucity of a good evidence base specific to pregnancy prevent the publication of specific guidelines. However, reference should be made to the comprehensive guidelines ‘The rare coagulation disorders – review with guidelines for management from the UKHCDO’ [96] and ‘UKHCDO Guidelines on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders’ [29].

Gynaecology

Menorrhagia

Menorrhagia or excessive menstrual bleeding, is a common clinical problem among women of reproductive age [100]. The reduction in family size by the

Table 1. Treatment of rare inherited bleeding disorders.

Deficient factor	Estimated prevalence	Plasma half-life	Therapy
Fibrinogen	1:1 000 000	2–4 days	SD plasma, fibrinogen concentrate
Prothrombin	1:2 000 000	2–3 days	SD plasma, FIX complex concentrate
FV	1:1 000 000	36 h	SD plasma
FV and FVIII	1:1 000 000	–	SD plasma
FVII	1:500 000	4–6 h	Recombinant FVII, FVII concentrate
FX	1:1 000 000	40 h	SD plasma, FIX complex concentrate
FXIII	1:2 000 000	11–14 days	SD plasma, FXIII concentrates

SD plasma, solvent/detergent plasma.

widespread use of contraception and sterilization has resulted in a significant increase in the number of periods women experience during their reproductive life. This in turn amplifies the problem of menorrhagia today. Menorrhagia is subjectively defined as a complaint of heavy cyclical menstrual bleeding occurring over several consecutive cycles [101]. Objectively, it is defined as a total menstrual blood loss of >80 mL per menstruation (using the alkaline haematin method) [102]. It is difficult to quantify menstrual blood loss objectively because it involves techniques that are specialized, time-consuming and require collection of sanitary material by women. As a result, assessment of menorrhagia in clinical practice is usually subjective and often relies on the description provided by the patient. This method is unfortunately inaccurate and there is lack of correlation between patient's impression and the objective assessment of actual volume of blood loss [102]. The pictorial blood assessment chart (PBAC) is a semi-objective method of assessing menstrual bleeding based on the number and saturation of sanitary pads and tampons used (Appendix 2). A pictorial chart score of >100 was shown to have a reasonable accuracy for identifying menorrhagia with a sensitivity of 86% and a specificity of 89% [103]. Although the validity of this chart has been debated [104], it is simple to use and is at present the best practical tool available for the assessment of menstrual blood loss.

It is estimated that approximately 30% of women complain of menorrhagia [105]. Annually about one in 20 women aged 30–49 years consult their general practitioner for this reason [106]. It is the main presenting complaint in women referred to gynaecologists and accounts for two-thirds of all hysterectomies [107]. Menorrhagia could be due to local or systemic causes; however, the underlying pathology remains unidentified in approximately 50% of cases [108,109].

Disorders of haemostasis are associated with menorrhagia. Although this association has long been recognized, the magnitude of these disorders as a possible cause of idiopathic menorrhagia has been underestimated. Women who are referred for investigation of menorrhagia are not routinely screened for coagulation disorders even when no pelvic pathology is identified. In a recent UK survey, only 13% of gynaecologists would request a standard clotting screen and 2% would test for VWD in a 35 year old with menorrhagia and no pelvic pathology [110]. Similarly, a US survey found that 17% of physicians would order BT determination for reproductive age women with menorrhagia and only 4%

would consider VWD as the cause of menorrhagia [111].

The use of PBAC should be considered in the assessment of menstrual blood loss for the diagnosis of menorrhagia and evaluation of the treatment outcomes (grade C, level IV).

Prevalence of inherited bleeding disorders in women with menorrhagia. Over the last decade, there have been international efforts to assess the prevalence of inherited bleeding disorders in women with menorrhagia. VWD is the most common inherited bleeding disorder worldwide with a prevalence of 1–2% in the general population [51,112]. A recent systemic review of 11 prevalence studies of VWD in 988 women with menorrhagia reported an overall prevalence of 13% (95% CI, 11–15.6%), with prevalence in individual studies ranging from 5% to 24% [113]. The prevalence was higher in the European studies compared with that in the North American studies [18% (95% CI 15–23%) vs. 10% (95% CI 7.5–13%); $P = 0.007$]. This was explained by the authors to be likely the result of differences between the studies in the method of assessing menstrual blood loss and of recruitment of the study population, their ethnic composition, and the laboratory criteria for diagnosis of VWD.

In addition to VWD, platelet disorders and clotting factor deficiencies have also been identified in women presenting with menorrhagia [114–117].

A significant proportion of women with idiopathic menorrhagia have an underlying bleeding disorder, the commonest being VWD. Therefore, testing for these disorders should be considered (grade B, level III).

Heavy, prolonged and irregular menstrual periods are frequent complaints in adolescent girls. This is likely to be due to immaturity of the hypothalamic–pituitary–ovarian axis resulting in anovulatory cycles [118–120]. However, in a significant proportion of these cases, an underlying bleeding disorder may be identified [121–124]. Eight of 14 adolescents presenting with menorrhagia without thrombocytopenia who underwent comprehensive testing for a bleeding disorder had an underlying bleeding disorder [121]. In a retrospective study of 106 adolescents with menorrhagia, 11 (10.4%) patients were found to have an underlying bleeding disorder. A positive family history of bleeding symptoms was a significant predictor of a bleeding disorder in this study [124]. Acute adolescent menorrhagia requiring hospital admission is also a strong predictor of a

bleeding disorder. A primary coagulation disorder was found in 19% of those admitted to a children's hospital for acute menorrhagia [125]. One quarter of those with haemoglobin $<10 \text{ g dL}^{-1}$, one-third of those requiring transfusion, and one-half of those presenting at menarche had such an underlying disorder. In another study of adolescents with menorrhagia requiring hospitalization, 15 (33%) of 46 cases had an underlying haematological disease, with VWD accounting for five cases [126].

Whether adolescent menorrhagia is more likely to be associated with bleeding disorders is uncertain. In a study of 115 women with menorrhagia, the frequency of an underlying bleeding disorder in adolescent, reproductive age, and perimenopausal women presenting with menorrhagia was found to be similar [127].

Menstruation may be the first haemostatic challenge faced by girls with an inherited bleeding disorder. Menorrhagia in these girls is usually severe and they often present acutely. This could be explained by the findings of increased VWF and FVIII levels with age [128,129].

Adolescents presenting with acute menorrhagia should be investigated for bleeding disorders. For prepubertal girls either known to have a bleeding disorder or a positive family history, plans should be made in anticipation of the possibility of acute menorrhagia at the onset of menarche (grade C, level IV).

Testing for inherited bleeding disorders in women with menorrhagia

Bleeding history. Testing for VWD and other bleeding disorders in all women with menorrhagia is neither practical nor necessary. The first step in investigating for an underlying bleeding disorder in these women is to take a focused personal and family history of bleeding symptoms. This can be used to identify women with significant additional bleeding symptoms suggestive of an underlying bleeding disorder [130]. The frequency of bleeding symptoms has been showed to be significantly higher in patients with VWD than in women without a bleeding disorder [115]. Significantly more women with VWD had menorrhagia since menarche (65%), compared with women without a bleeding disorder (9%). Bleeding after tooth extraction, and postpartum and postoperative bleeding were also more common among women with VWD [115].

Bleeding history should include [131]:

- 1 Excessive menstrual bleeding since menarche;
- 2 History of PPH, surgery-related bleeding or bleeding associated with dental work;

- 3 History of bruising $>5 \text{ cm}$ one to two times per month, epistaxis one to two times per month, frequent gum bleeding, family history of bleeding symptoms.

[A 'positive screen' entails any one from 1 or 2, or two or more from 3.]

Initial investigation for an underlying bleeding disorder in women with menorrhagia should consist of a focused personal and family history of bleeding symptoms (grade C, level IV).

Laboratory testing:

1. Full blood count and ferritin.

The initial laboratory evaluation for an underlying bleeding disorder should consist of full blood count (FBC) and serum ferritin, which will exclude thrombocytopenia and assess the degree of anaemia. If the detailed history identified a 'positive screen' and the platelet count is normal, then a stepwise sequence of testing for various bleeding disorders should be carried out. This also applies to women who are considering major surgical intervention, regardless of the presence of a positive screen [130]. It is essential for these testing to be undertaken in settings where necessary expertise and resources are available on-site to ensure appropriate and accurate diagnosis.

2. PT and activated PTT.

PT and activated PTT (APTT) are standard tests of haemostasis, which are carried out as part of the initial evaluation. However, they have poor sensitivity, specificity and both positive and negative predictive values for an underlying bleeding disorder [132]. Normal PT and APTT do not exclude an underlying bleeding disorder, but they should be adequate for screening for the severe rare clotting factor deficiencies [133]. A mixing study should be performed in cases of prolonged APTT to distinguish between a deficiency state and an inhibitor.

3. von Willebrand screen.

This includes VWF:Ag, VWF:AC and FVIII levels (FVIII:C). FVIII level can be reduced in VWD as VWF protects FVIII from proteolytic cleavage [134]. Comprehensive guidelines on the diagnosis of VWD have been produced by the UKHCDO [135].

Difficulties in diagnosing type 1 VWD because of its variable expression influenced by genetic and environmental factors are well established [136,137]. These factors include women's race, ABO blood group, phase of the menstrual cycle and the use of oral contraceptives.

At present, there is a lack of consensus in the literature supporting a true variation of VWF levels during the menstrual cycle. Initial studies have suggested a decrease in VWF and FVIII levels during

menstruation [138–140]. A longitudinal study of 39 healthy Caucasian women sampled on days 2, 8, 15 and 21 showed a strong cyclic variation with a decrease in VWF values in the early follicular phase and peak values in the luteal phase [129]. However, another longitudinal study of 95 healthy women sampled serially at days 4–7, 11–15 and 21–28, did not find this variation [141]. A recent cross-sectional study of 90 controls and 85 women with menorrhagia, assigned into groups that were more finely divided in the sampling time during the menstrual cycle, found the lowest VWF levels on days 1–4 and the highest on days 9–10 [142]. Due to the inconsistencies in these results, recommendations for testing exclusively during menses cannot be made. However, the time of testing in relation to the menstrual cycle should be noted, and if the results from the initial testing were borderline or just below the normal range, repeat testing during days 1–4 of the menstrual cycle would be advisable.

It is currently not clear whether the concurrent use of COC would obscure the diagnosis of VWD. It has been observed that oestrogen increases VWF levels [143]. There has been report of COC use masking the diagnosis of VWD [144]. A review of the literature on the effect of COCs on coagulation factors reveals large variations of study designs and results [145]. The majority of the studies demonstrated an increase in fibrinogen, prothrombin, FVII, FVIII and VWF whilst other factors, such as FV, FIX and FXIII, did not seem to be affected. The effect appears to be related to oestrogen, dose dependent, and appreciable above a dose of 50 µg of ethynylestradiol. The effect of smaller doses of oestrogen, which are commonly used today, is less and may not be significant. In a study of 20 non-pill users and 20 women on low-dose COC (≤30 µg), no significant difference between the mean values of APTT, fibrinogen, FVIII:C, VWF:Ag, VWF:AC and FXI were found [129]. Due to lack of evidence presently demonstrating a definite effect of COC on VWF levels, a practical approach would be to still test women when on COC, especially if they are still experiencing menorrhagia. Repeat testing off COC should however be considered if results are borderline or in the lower half of the normal range.

Patients with blood type O have 25% lower VWF levels compared with other blood types [146]. This means if VWD testing is adjusted for the ABO blood type, a lower VWF level would be required as a cut off for the diagnosis of VWD for blood type O patients. Consequently, this would exclude blood type O patients with subnormal level defined as two

standard deviations below the mean of the total population (i.e. <50 IU dL⁻¹), but a level within the normal range for blood type O patients (i.e. >35 IU dL⁻¹). However, type O patients with VWF levels between 35 and 50 IU dL⁻¹ were found to have similar bleeding symptoms as non-O patients in that range [147]. Therefore, the use of ABO adjusted ranges for VWF levels may not be necessary because bleeding symptoms seem to depend on the VWF level regardless of the blood type.

4. Platelet function analysis.

Neither BT nor platelet function analyser (PFA-100) are effective screening tests for mild VWD and platelet function disorders [148–150]. However, they can be performed concurrently with VWF testing as a baseline and used for monitoring postintervention to ensure adequate haemostasis.

If all initial haemostasis testing and complete gynaecological evaluation are normal, platelet aggregation and release studies should be considered. A relatively high prevalence of platelet function abnormalities was recently reported in women with menorrhagia [117,127]. Amongst 74 women with unexplained menorrhagia, platelet aggregation and platelet ATP release were decreased with one or more agonist in 35 (47.3%) and 43 (58.1%) women respectively. The prevalence odds of platelet aggregation abnormalities was found to be 4.2-fold higher among women with menorrhagia than control women [117].

5. Other clotting factor levels.

If the VWD (including FVIII) screen and platelet function analysis are both normal, depending on the degree and severity of additional personal bleeding symptoms and the family history, testing for additional coagulation deficiencies (FV, FVII, FIX, FXI and FXIII) should be considered.

6. Non-haematological tests.

There is some evidence linking hypothyroidism with menorrhagia [151–153]. Thyroid function tests should be considered if the patient is symptomatic.

Laboratory testing for an inherited bleeding disorder should be carried out if the woman presenting with menorrhagia has a positive bleeding history or if surgical intervention is planned (grade C, level IV).

Laboratory testing should only be undertaken in settings where necessary expertise and resources are available on-site to ensure appropriate and accurate diagnosis (grade C, level IV).

Laboratory testing should be carried out in the following stepwise sequence (grade C, level IV):

- 1 FBC and ferritin;
- 2 PT and APTT;
- 3 von Willebrand screen (VWF:Ag, VWF:RCO and FVIII:C) Testing exclusively during menstruation, off COC or adjusted for blood type is not necessary at the initial evaluation. However, these details should be documented and repeat testing should be considered if the results are borderline.
- 4 Platelet function analysis (platelet aggregation and release studies);
- 5 Other clotting factor levels;
- 6 Thyroid function tests if symptomatic.

Menorrhagia in women with inherited bleeding disorders Menorrhagia has been well recognized as a common symptom in women with inherited bleeding disorders including VWD, other clotting factor deficiencies and platelet disorders [27,99,154–156]. In a review of the obstetric and gynaecological manifestations of bleeding disorders, menorrhagia was reported in 32–100% of women with type I VWD and in 10–70% of women with other bleeding disorders [157]. In a study of 38 females with type I VWD, menorrhagia was the most common bleeding symptoms, occurring in 93% of adult women [155]. Using the PBAC to assess menstrual blood loss, menorrhagia (PBAC score >100) was confirmed in 74%, 59% and 57% of women with VWD, FXI deficiency and who were carriers of haemophilia respectively [154]. The duration of menstruation was also found to be significantly longer and episodes of flooding more common in women with inherited bleeding disorders compared with the control group ($P = 0.001$).

Menstruation has a major influence on women's lifestyle and employment. Menorrhagia has been found to have a negative effect on the quality of life in women with inherited bleeding disorders [158]. In the same study, 39% of these women had to cut down on the time they spent on their work or other activities, 47% felt they had accomplished less than they would like during this period, and 38% felt they were limited in the kind of work they could do [158]. The impact of menstruation on young women in terms of restrictions in sport activity, travel, work, studies and sex is also substantial [159]. Although these comments were made in regard to the impact of menses in general, this effect is likely to be even greater in women with an inherited bleeding disorder and excessive menstrual bleeding. Early recognition, accurate diagnosis and appropriate management will help to improve not only the quality of care for these women but also their quality of life.

Menorrhagia is one of the most common bleeding manifestations in women with inherited bleeding disorders and has a negative effect on their quality of life (grade B, level III).

Management of menorrhagia in women with inherited bleeding disorders A multidisciplinary clinic, including both haematologist and gynaecologist, set up within the network of haemophilia treatment centres (HTCs) is ideal for providing comprehensive care for the management of menorrhagia in women with inherited bleeding disorders. This ensures appropriate and accurate on-site haemostasis testing; avoids communication problems between professionals; allows clear management plans to be made (and competent completion of desmopressin test dose); and can address the psychosocial aspects related to bleeding disorders.

In a survey by the Centers for Disease Control and Prevention in the USA, 95% (71 of 75) of women receiving care in HTCs reported a strong positive opinion and satisfaction [160]. Similar positive findings were found among patients of the multidisciplinary clinic at the Katharine Dormandy Haemophilia Centre of the Royal Free Hospital in London [161].

Menorrhagia in women with an underlying bleeding disorder is likely, but not exclusively, to be due to a defect in haemostasis. The cause of menorrhagia may be multifactorial in these women. In a survey of women with VWD, half of the women undergoing hysterectomy for menorrhagia had additional uterine pathology such as fibroids or endometriosis [162]. Therefore, a thorough gynaecological evaluation should be performed to exclude pelvic pathology, especially the possibility of malignancy in older women.

The Royal College of Obstetricians and Gynaecologists has produced management guidelines of menorrhagia in general [102,107]. Most of these have not been assessed in menorrhagia related to an underlying bleeding disorder, but for best clinical practice, the results for general menorrhagia patients can be extrapolated.

Management of bleeding disorder-related menorrhagia involves consideration of the patient's age, childbearing status and preference in terms of perceived efficacy and side-effect profile. Therapeutic options for the control of menorrhagia in women with underlying bleeding disorders include medical treatments [such as anti-fibrinolytics (tranexamic acid), intranasal and subcutaneous DDAVP, oral contraceptives, levonorgestrel (LNG) intrauterine

device and clotting factor replacement] and surgical treatments (such as endometrial ablation and hysterectomy). They are similar to the treatment options for menorrhagia in general with the exception of DDAVP and clotting factor replacement. However, management of women with inherited bleeding disorders requires additional monitoring of the haemostatic parameters and awareness of the increased risk of bleeding with any surgical interventions.

Management of menorrhagia in women with inherited bleeding disorders should be provided by a multidisciplinary team including a haematologist and gynaecologist (grade C, level IV).

Medical treatment of menorrhagia

Tranexamic acid Increased uterine fibrinolytic activity is found in women with menorrhagia compared to those with normal menstrual loss; this increased fibrinolysis is most likely due to high levels of endometrium-derived plasmin and plasminogen activators [163,164]. Tranexamic acid is an antifibrinolytic agent that reversibly blocks lysine-binding sites on plasminogen and prevents fibrin degradation [165]. Endometrial tissue plasminogen activator (t-PA) levels were significantly lower after three treatment cycles in 12 menorrhagic women who received tranexamic acid 500 mg four times daily for 5 days [166]. In another study, tranexamic acid, 1 g three times daily for 5 days, was also shown to significantly reduced t-PA and plasmin activity in the menstrual as well as in the peripheral blood of menorrhagic women, compared with pretreatment values [163].

Several studies of variable design have been carried out to assess the therapeutic efficacy of tranexamic acid in the treatment of idiopathic menorrhagia [166–170]. Using oral tranexamic acid ranging from 500 mg or 1 g four times daily for 4–7 days per cycle, the menstrual blood loss was reduced by 34–59% over two to three cycles in women with menorrhagia. Tranexamic acid has been shown to be more effective than NSAIDs in the reduction of menstrual loss; 54% vs. 20% when compared with mefenamic acid [170], and 44% vs. 20% when compared with flurbiprofen [168]. However, none of them affected the duration of menses [168,170].

Oral tranexamic acid is generally well tolerated by women with menorrhagia. Nausea and diarrhoea are the most common side effects. The Cochrane systematic review of antifibrinolytics for heavy menstrual bleeding concluded that adverse events during

treatment with tranexamic acid were no higher than with placebo, NSAIDs, cyclic progestogens or ethamsylate [171]. There have been some concerns with the use of tranexamic acid due to isolated reports of thromboembolic complications, which may have led to the reluctance in its use. However, the incidence of thrombosis, over a 19-years time frame and 238 000 patient-years of treatment with tranexamic acid, has been shown to be similar to the spontaneous frequency of thrombosis in women in the general population [172]. Nonetheless, the use of tranexamic acid is contraindicated in patients with a history of thromboembolic disease.

Royal College of Obstetricians and Gynaecologists (RCOG) guidelines recommend tranexamic acid for 3 months as a first-line medical treatment for menorrhagia [101]. If successful, tranexamic acid can be used indefinitely in patients not requiring contraception or who prefer non-hormonal treatment. In women with bleeding disorder, tranexamic acid has been widely used (orally, intravenously, topically alone or as an adjuvant therapy) in the prevention and management of oral cavity bleeding, epistaxis, gastrointestinal bleeding and menorrhagia. However, there is a lack of objective data on its efficacy in the reduction of menstrual loss in this population.

The recommended oral dose of tranexamic acid for the treatment of menorrhagia is 1 g three to four times daily for 3–4 days (maximum total daily dose of 4 g) [173]. It should be initiated once menstruation has started. There has been report on successful use of a single high-dose (4 g daily) therapy in three types 2A and 2B VWD patients, but this regime can be associated with severe nausea and vomiting [174].

Combined oral contraceptives Combined oral contraceptives are a highly reliable method of birth control. They are also useful for cycle regulation and reduction in the incidence of dysmenorrhoea and premenstrual tension. There is some evidence that COC significantly reduces menstrual blood loss in women with and without menorrhagia [175,176]. In a trial of a 50 µg ethinylestradiol pill, menstrual loss was reduced by 52.6% in 68% of 164 women with objective menorrhagia [177]. The efficacy of low-dose COC in reducing menstrual blood loss has been assessed in only one randomized controlled trial. However, the trial was not placebo controlled and was relatively small (45 women, seven did not complete the trial) [178]. There was a significant reduction in menstrual loss in the COC group (43%, $P \leq 0.001$), as well as in the low-dose danazol (49%, $P = 0.006$) and the mefenamic acid groups (38–

39%, $P = 0.002$). FVIII and VWF levels have been shown to increase with the use of high-dose (50 μg oestradiol) pills [145] but not with the currently standard, lower-dose (30 μg oestradiol) pills [129].

The efficacy of COC in reducing menstrual blood loss in women with bleeding disorders is unknown. In a survey of women with VWD (types 2 and 3) unresponsive to DDAVP, COC was reported to be an effective treatment of menorrhagia in 88% of the women [62]. On the other hand, in type I patients, a standard dose and a higher dose COC were effective in only 24% and 37% of the cases respectively [162].

Traditionally COC is administered daily for 21 days, followed by a pill-free week during which uterine bleeding occurs. In recent years, the extended or continuous administration of COC (>28 days of active pills) has been reported as a successful regime in the treatment of endometriosis, dysmenorrhoea, and other menstruation-association symptoms [179–182]. Avoidance of menstruation through continuous dosing of COC has potential benefits which include less interference with daily activities or special events and less menstruation-related absenteeism from work or school [183,184]. The Cochrane systematic review of continuous versus cyclical use of COC concluded that both regimes have similar patient satisfaction and discontinuation rates [185]. It also showed that continuous COC administration has similar, if not better, effect on improving bleeding patterns and may improve menstruation-associated symptoms. This regime could be very helpful in the management of menorrhagia in women with bleeding disorders as this regime allows women to control the timing and reduce the frequency of their menstruation. It may also be more effective than the cyclical regime in reducing menstrual blood loss.

Increased risk of thrombosis is the main concern associated with the use of COC. However, women with bleeding disorders have a low inherited thrombotic risk. Serious side effects of COC include hypertension and, rarely, impaired liver function and hepatic tumours. Other less serious side effects include nausea, vomiting, headache, breast tenderness, breakthrough bleeding, fluid retention, depression and skin reactions.

Desmopressin Desmopressin (1-desamino-8-D-arginine vasopressin, DDAVP) is a synthetic analogue of the antidiuretic hormone vasopressin. It increases plasma concentration of FVIII and VWF through endogenous release [186–188]. It is an important therapeutic alternative to plasma-derived coagulation products because it is effective in selected cases

and avoids the risks of infection with blood-borne viruses. A test dose is recommended before treatment to assess its effectiveness as the response is not universal. DDAVP has been shown to be effective in the prevention and treatment of bleeding episodes in patients with mild VWD and haemophilia A. It can also be used in patients with platelet disorders because of its effect on increasing platelet adhesiveness [189].

Desmopressin is available in several formulations. It can be administered parenterally via intravenous or subcutaneous injection, or nasally as a spray. The chosen route of administration is dependent on the purpose of its use and the magnitude of the effect required. The optimal haemostatic effect of DDAVP is achieved with a dosage of 0.3 $\mu\text{g kg}^{-1}$, which increases plasma FVIII and VWF levels two- to sixfold after intravenous administration [190]. It is usually given over 20 min as slow intravenous infusion. Typically the 4 $\mu\text{g mL}^{-1}$ solution is made up in 50–100 mL normal saline for infusion. When given subcutaneously in the same dose (0.3 $\mu\text{g kg}^{-1}$), the response is of similar magnitude to that of intravenous administration, but peak levels are reached later [191]. A more concentrated solution (15 $\mu\text{g mL}^{-1}$) is available for subcutaneous use although it does not have a product license in the UK. Intranasal administration of DDAVP is an attractive route because it allows patients to treat themselves at home without delay in the event of bleeding episodes, e.g. at the onset of menstruation, and without the use of needles [192,193]. The effect of intranasal administration of 300 μg with a metered-dose spray is comparable with that of 0.2 $\mu\text{g kg}^{-1}$ intravenous injection, and the reproducibility of the haemostatic effect is similar to that of intravenous injection [186,194].

There are few side effects of DDAVP related to its vasomotor effects. They include mild tachycardia, headache and flushing. Due to the antidiuretic effect of DDAVP, there is a small risk of hyponatraemia and potentially water intoxication. This complication can be greatly reduced by restriction of fluid intake and close electrolyte monitoring, especially in those receiving multiple doses of DDAVP.

The influence of nasal DDAVP on the local fibrinolytic activity in the endometrium and on menstrual blood loss is interesting. Increased local fibrinolytic activity in the endometrium and menstrual fluid has been demonstrated in women with menorrhagia [195,196]. Tissue-PA is the main physiological activator of the fibrinolytic system in blood and in the endometrium. DDAVP has been shown to

increase t-PA in the circulation [187,188], but in one study, it did not increase the fibrinolytic activity (plasmin levels) in the menstrual fluid [195].

Case series have shown that subcutaneous [197] and intranasal DDAVP [198] are effective in the management of menorrhagia in women with bleeding disorders who respond to DDAVP. Based on women's subjective assessment of reduction in menstrual flow, the efficacy of DDAVP was reported as excellent or good in 86% and 92% of women treated with subcutaneous and intranasal DDAVP, respectively [197,198]. However, in a randomized placebo-controlled crossover trial using PBAC, intranasal DDAVP was not significantly ($P = 0.51$) different from placebo in reducing PBAC scores [199]. There was a statistically significant reduction in the PBAC score ($P = 0.0001$) in both groups compared with pretreatment score and a trend towards a lower score when using intranasal DDAVP. It is possible that this difference did not reach statistical significance due to small sample size. No statistically significant difference was found in measures of quality of life for either group in this study. In another randomized crossover study, the reduction in menstrual blood loss with DDAVP, in women with menorrhagia and prolonged BT, was not significantly different from either baseline or placebo [200]. However, there was a significant reduction in the mean blood flow during the 2 days of DDAVP treatment and in the total menstrual blood loss when DDAVP was combined with tranexamic acid. It is possible that tranexamic acid counteracts the increased fibrinolytic activity (t-PA) induced by DDAVP.

Currently, there is no consensus regarding the optimum dose and duration of nasal DDAVP for treatment of menorrhagia in women with bleeding disorders. Most studies have used high-dose DDAVP intranasal spray (1.5 mg mL^{-1}) once daily; administered as $150 \text{ }\mu\text{g}$ (one intranasal spray) for patients weighing $\leq 50 \text{ kg}$ and $300 \text{ }\mu\text{g}$ (two intranasal sprays; one per nostrils) for patients weighing $>50 \text{ kg}$. Additional doses within a 24-h period will require specialized and individual assessment. The response to test dose should be clearly documented. DDAVP is usually given during the first 2–3 days of the menstrual period. This is based on the finding that 90% of all menstrual flow occurs during the first 3 days [201]. However, the pattern of menstruation may be different in women with bleeding disorders. In one study, these women bleed heavily throughout their menstruation [154]. As a result, dose and duration of treatment may have to be adjusted depending on the PBAC scores.

Other medical treatments Progestogens. Oral progestogens are one of the most commonly prescribed medications for menorrhagia [202]. There are two different cyclical regimes of oral progestogens: a short luteal phase treatment (days 19–26 or 15–25) or a longer 21-days course starting from day 5 of the cycle. A Cochrane systematic review, including six randomized controlled trials of the short luteal phase oral progestogen therapy, showed this regime to be significantly less effective in reducing menstrual blood loss when compared with danazol, tranexamic acid and progesterone releasing intrauterine system (IUS) [203]. A single trial comparing a long 21-day course (norethisterone 5 mg three times daily) with LNG-IUS showed significant reduction in menstrual blood loss in both group, but oral progestogen was less effective and acceptable by patients when compared with LNG-IUS [204]. No randomized, controlled trials comparing progestogen treatment with placebo were identified.

Cyclical 21-days progesterone therapy can be considered as a second-line treatment for patients who do not respond to other medical therapies previously discussed or in whom such treatments are contraindicated. However, the compliance of this regime is usually not good due to progestogenic side effects. These include fatigue, mood changes, weight gain, bloating, headaches, depression, irregular bleeding and adverse effect on bone density and lipid profile.

Oral progestogens in high doses alone, or in combination with DDAVP or clotting factor concentrate, may be useful in the treatment of acute menorrhagia in women with inherited bleeding disorders. Other forms of progestogens, injections or implants, have not been evaluated in women with menorrhagia, but studies in women without menorrhagia have shown that a considerable proportion of women experience amenorrhoea with such therapies. More research is needed before recommendation can be made for women with menorrhagia with or without associated bleeding disorders.

Nonsteroidal anti-inflammatory drugs. NSAIDs (e.g. mefenamic acid and naproxen) have been shown to be more effective than placebo in reducing menstrual blood loss but less effective than either tranexamic acid or danazol [205]. NSAIDs have the added advantage of reducing menstrual pain and menstrual migraine. However, their use is contraindicated in women with inherited bleeding disorders due to their anti-aggregator effect on platelet function. This highlights the need for awareness of inherited bleeding disorder as a potential cause of

menorrhagia in order to avoid the use of NSAIDs in such cases.

Ethamsylate. Ethamsylate is a haemostatic agent that maintains platelet and capillary integrity and affects prostaglandin synthesis. In the only randomized controlled trial in women with menorrhagia in general, this treatment showed no reduction in menstrual blood loss when used during menstruation, compared with 20% and 54% reduction found with mefenamic acid and tranexamic acid respectively [170]. There are no data on the efficacy of this treatment in women with bleeding disorders, but in view of its mode of action, it may have a different effect on heavy menstrual loss in these women, which warrants further studies.

Danazol and gonadotrophin-releasing hormone. Danazol and gonadotrophin-releasing hormone (GnRH) agonists are effective in reducing menstrual loss and duration of menstruation. Data on their effectiveness in the treatment of menorrhagia related to bleeding disorders are lacking. Their side effects and risks, because of the resulting hypoestrogenic state, make them less acceptable for long-term use. They are more expensive than other medical treatments of menorrhagia. GnRH agonists with simultaneous add-back therapy with either tibolone or combined oestrogen/progesterone may be an alternative option to surgery for women with severe bleeding disorders, e.g. type 3 VWD, and menorrhagia not responding to other treatments.

Levonorgestrel-releasing intrauterine device

The LNG-IUS (trade name Mirena) is an intrauterine system with a T-shaped plastic frame 32-mm long and a reservoir on the vertical stem of the IUS containing 52 mg of LNG. It releases 20 µg of LNG every 24 h over a recommended duration of use of 5 years. It suppresses endometrial growth causing the glands of the endometrium to become atrophic and the epithelium inactive [206]. It was originally developed as a contraceptive device. Despite it being such a novel intervention, it has rapidly become very popular. In a systematic review, LNG-IUS was shown to reduce the average menstrual blood loss by 74–97% after durations of use between 3 and 12 months [207]. It is an attractive treatment option for women who require contraception and wish to preserve their fertility and for those who are unlikely to comply with drug treatments.

The Cochrane systematic review revealed LNG-IUS to be more effective in the treatment of menorrhagia in general compared with oral norethisterone given during days 5–26 of the menstrual cycle (94%

reduction in menstrual blood by LNG-IUS vs. 87% by oral norethisterone) and associated with higher rates of satisfaction and continuation with treatment (77% vs. 22%) [204,208]. The LNG-IUS was also found to produce significantly greater reductions in menstrual blood loss (measured by the alkaline haematin method, weighing sanitary materials before and after use, and PBAC scores) than mefenamic acid [209]. Another trial compared LNG-IUS with the existing medical treatment (prostaglandin synthesis inhibitors or fibrinolysis inhibitors) the women were receiving while waiting to undergo hysterectomy for treatment of excessive menstrual bleeding [210]; 64% of women in the LNG-IUS group decided to cancel hysterectomy at 6 months compared with 14% in the group who continued with their existing medical treatment ($P = 0.001$). All quality of life scores were significantly higher in the LNG-IUS group at 6 months ($P = 0.002$).

When compared with endometrial ablation (either transcervical resection or balloon ablation), LNG-IUS appears to be less effective in the treatment of menorrhagia [208]. A significantly larger proportion of women with ablation had successful treatment (as measured by a PBAC score of <75) than those with LNG-IUS (92% versus 75%; $P = 0.0006$). However, there was no significant difference in rates of satisfaction with treatment (LNG-IUS: 77.3% and ablation: 84.3%) or haemoglobin values after treatment [208]. Endometrial ablation may provide a quicker resolution to menstrual symptoms, but it requires the use of operation facilities and anaesthesia, and is not suitable for women who want to preserve their fertility. The LNG-IUS requires less skill, can be inserted in outpatient, and is an effective reversible contraception.

The LNG-IUS was compared with hysterectomy in one trial to assess the effects on quality of life and cost-effectiveness [211,212]. The health-related quality of life improved significantly in both groups and there were no significant differences in outcome measures at 12 months except that women with hysterectomy suffered less pain ($P = 0.01$). Although 20% and 42% of women in the LNG-IUS group had undergone hysterectomy by 12 months and 5 years of follow up, respectively, the mean costs of treatment for this group of women were significantly lower than the group who had hysterectomy.

The side effects include those related to an intrauterine device, for example, irregular bleeding and expulsion of the device [208]. The commonest side effect is irregular bleeding or spotting in the first 3–6 months after insertion. It usually settles after 6–12 months in the majority of cases. Amen-

orrhoea is also commonly reported; 44% of the women had no bleeding after 6 months in one study [213]. Therefore, appropriate counselling on the potential changes in the bleeding pattern may help to improve its acceptability. The expulsion rates (5–10%) are similar to other intrauterine devices [214,215]. The overall discontinuation rate for the LNG-IUS was 20% in randomized controlled trials and 17% in the case series [207]. Other side effects of LNG-IUS include those related to the systematic effects of progestogens, such as weight gain, bloating, breast tenderness, greasy hair or skin, acne, nausea, mood changes and depression. Nevertheless, it is better tolerated than systemic progestogens.

The long-term (5 years) efficacy of LNG-IUS for contraception is well established [214]. However, data on its long-term efficacy in the treatment of menorrhagia is limited. The LNG-IUS was found to induce atrophy of the endometrial epithelium for more than 5 years [206], which provides a rationale for the reduction of menstrual blood loss for a prolonged period of time. An observational study has demonstrated a continuation rate of 50% after a mean 54 months of follow up. Amongst these women, 57% have occasional bleeding and 35% have amenorrhoea [216]. Significant reduction in menstrual blood loss and increase in haemoglobin and serum ferritin levels were shown to sustain for as long as 36 months in women with idiopathic menorrhagia [217]. Further studies are needed to establish the long-term efficacy of LNG-IUS in the reduction of menstrual blood loss.

The use of LNG-IUS in women with inherited bleeding disorders has been evaluated in 16 women (13 VWD, two FXI deficiency and one Hermansky–Pudlak syndrome) with menorrhagia not responding to medical treatment [218]. After 9 months, the PBAC score had decreased significantly from a median of 213 (range 98–386) to 47 (range 24–75) and the haemoglobin concentrations had increased significantly from a median of 12.1 (range 8.0–13.2 g dL⁻¹) to 13.1 (range 12.3–14 g dL⁻¹) ($P = 0.0001$). Nine women became amenorrhoeic. No side effects were reported, except irregular spotting, which ranged from 30 to 90 days (median 42 days). Most (11) women did not feel that the irregular bleeding affected their life and the remaining five were only slightly affected. Prior to the insertion of the LNG-IUS, all women had at least 1 day per month where their life was significantly affected by their periods, with six women reporting at least 3 days were affected. Nine months after insertion of LNG-IUS, none of them had any days of the month

when their menstruation significantly affected their life. All women in this trial had mild to moderate bleeding disorders; therefore, further studies are required to evaluate the effectiveness of LNG-IUS in women with severe factor deficiencies.

Women with bleeding disorders could potentially be at risk of bleeding at the time of insertion. Adequate haemostatic coverage is recommended especially in women with severe forms of bleeding disorders.

Clotting factor Clotting factor replacement, with either recombinant or plasma-derived factor concentrate, will be required in some women with bleeding disorders, especially in adolescents [122] and those with severe deficiency or when they present acutely. A multidisciplinary assessment approach by haematologists and gynaecologists is crucial in the management of these women.

Medical treatment of menorrhagia in women with inherited bleeding disorders include tranexamic acid, COCs, DDAVP, cyclical 21-days oral progesterone, and the LNG-IUS. The treatment choice depends on the type of bleeding disorder, and patient's age, childbearing status and preferences in terms of the perceived efficacy and side effects (grade C, level IV).

Specific haemostatic therapy will be required in some women with inherited bleeding disorders to control menorrhagia. A multidisciplinary approach in the management of these individuals is essential to ensure optimal outcomes (grade C, level IV).

Surgical treatment for menorrhagia

Surgical intervention may be required in some women who do not tolerate medical treatments or where such treatments have failed. An underlying bleeding disorder can potentially be the reason for failed medical therapy [219]. Surgery may also be indicated in the presence of a pelvic pathology.

Women with inherited bleeding disorders are at greater risk of bleeding complications from surgery, including increased perioperative and delayed (7–10 days after surgery) bleeding. Prophylactic treatment is recommended in women with bleeding disorders. Close follow up for at least 10 days postsurgery is also recommended to monitor specific factor levels and to assess for delayed bleeding complications such as wound breakdown. Multidisciplinary care by haematological, gynaecological/surgical and anaesthetic teams is essential to ensure

an optimal outcome. Any surgical intervention in women with bleeding disorders should be carried out by experienced professionals. Extra care should be taken in ensuring adequate haemostasis and the use of surgical drains should be considered.

Hysterectomy Hysterectomy is an established, effective and definitive treatment for menorrhagia associated with high patient satisfaction. However, hysterectomy is a major surgical procedure with significant physical and emotional complications and social and economic costs. A large cohort study evaluated 37 298 hysterectomies performed for benign indications in the UK in 1994 and 1995 with a 6 week postsurgery follow up and found the associated mortality rate to be 0.38 per 1000 (95% CI, 0.25–0.64) [220]. The overall operative complication rate was 3.5% (3% severe) and postoperative complication rate was 9% (1% severe) [220,221]. Hysterectomy also has a risk of long-term complications, including early ovarian failure, and urinary and sexual problems. For these reasons, less invasive alternatives (e.g. endometrial resection and ablation) have been developed for the treatment of menorrhagia.

Endometrial ablation Endometrial ablative techniques, which destroy the lining of the uterus, are increasingly used today as an effective alternative to hysterectomy for the management of heavy menstrual bleeding. They have a shorter operating time and hospital stay, quicker recovery and fewer postoperative complications than hysterectomy [222]. In recent years various endometrial ablative techniques have evolved. The first generation techniques (resection, laser and rollerball) were introduced in the 1980s. They are performed under direct vision and require specialized surgical skills. The second generation techniques are designed to ablate the full thickness of the endometrium by controlled application of heat, cold, microwave or other forms of energy. They require sophisticated equipment and are mostly performed blindly. A systematic review reported that, in general, they are technically simpler and quicker to perform than first generation techniques, while satisfaction rates and reduction in menstrual blood loss are similar [223]. Second generation techniques are also less invasive, therefore, they may be a safer option for women with bleeding disorders. Although existing evidence suggests that the complication profiles of the newer techniques compare favourably to the first generation techniques, long-term data on the safety of these newer techniques are still unavailable.

One study evaluated thermal balloon ablation in 70 women with severe menorrhagia and severe systematic disease, including 25 with 'coagulopathy' [224]. The procedure was performed under local anaesthesia and the success rate was over 90% at 3 years follow up. The findings of a smaller retrospective study, which assessed the efficacy of endometrial ablation in seven women with VWD-related menorrhagia, were less favourable [225]. Four women experienced recurrence of menorrhagia after a median of 8 months postablation, and three of them eventually underwent hysterectomy at a median of 11 months postablation.

Consideration for the presence of an underlying bleeding disorder may be warranted in women who 'fail' endometrial ablations or continue to have excessive menstrual bleeding after an ablation. Prophylactic treatment should always be considered to prevent bleeding complications. Guidance regarding the selection and use of therapeutic products for surgery in patients with VWD and other hereditary bleeding disorders can be obtained from the UKHCDO guidelines [29,67].

Prophylactic treatment should be considered in women with inherited bleeding disorders undergoing surgery for treatment of menorrhagia. The surgery should be performed by experienced professionals with special attention to haemostasis. The use of a surgical drain should be considered (grade C, level IV).

Other gynaecological problems in women with inherited bleeding disorders

Women with bleeding disorders are at risk of the same gynaecological problems that affect all women, possibly with higher risks for conditions that are associated with bleeding [157].

Haemorrhagic ovarian cysts A recent review identified 15 studies, mostly case reports and case series, reporting one or more haemorrhagic ovarian cysts in women with inherited bleeding disorders [157]. In one study, the prevalence was found to be 6.6% (nine of 136 women with VWD) [226]. In another study, two cases of spontaneous broad ligament haematomas were reported in a series of eight women with VWD [27]. Women with bleeding disorders appear to be more vulnerable to bleeding from ruptured ovarian follicles. During ovulation, the ovum is expelled from the ovarian follicle into the peritoneal cavity. This process is usually not associated with any significant amount of bleeding,

but this risk is likely to be increased in women with bleeding disorders. As a result excessive bleeding can occur into the peritoneal cavity, the residual follicle or corpus luteum forming a haemorrhagic ovarian cyst, or the broad ligament resulting in a retroperitoneal haematoma.

In a survey of 81 menstruating women with type I VWD, 60 reported mid-cycle Mittelschmerz pain at a median intensity of 4 on a scale of 1–10, similar to the pain that accompanied their menstrual cycle [162]. Two-thirds of the cycles associated with mid-cycle pain have ultrasonically demonstrated pelvic fluid [227]. This suggests that Mittelschmerz is associated with bleeding at ovulation and could explain the large proportion of women with VWD suffering from it.

Haemorrhagic ovarian cysts in women with bleeding disorders may respond to clotting factor replacement therapy [228]. Conservative management is preferable in these women as surgery can lead to further damage, especially in cases with broad ligament haematoma. Surgical intervention, however, may be necessary in some cases and it is important to give appropriate prophylaxis in such cases.

Recurrences of haemorrhagic ovarian cysts can itself be a manifestation of a bleeding disorder [229]. COCs have been shown to inhibit ovulation [230]; therefore, can be used to prevent recurrences of haemorrhagic ovarian cysts [229,231,232]. In women with recurrent ovulation bleeding who wish to conceive, ovarian tracking with replacement therapy at the time of ovulation can be considered.

Endometriosis Endometriosis is a painful inflammatory condition characterized by the presence of endometrial tissue at ectopic sites. Several studies have demonstrated increased rates of endometriosis in women with heavier menses [233] presumably due to the increased rate of retrograde menstruation, a probable aetiology of endometriosis [234]. Thus women with bleeding disorders who have menorrhagia would similarly be at increased risk. In a survey of 102 women with VWD, 30% reported a history of endometriosis compared with 13% of controls [250]. Whether identification of bleeding disorders and appropriate intervention to reduce the menstrual loss would have an impact on the rate of endometriosis is currently unknown.

Dysmenorrhoea Dysmenorrhoea (pain or discomfort during or just before a menstrual period) is a common gynaecological complaint. It has been classified into primary or secondary dysmenorrhoea. Primary dysmenorrhoea occurs in the absence of

organic pathology and usually begins during adolescence. The prevalence of dysmenorrhoea is highest amongst adolescent women, with estimates ranging from 60% to 93%, depending on the measurement method used [235–238].

Secondary dysmenorrhoea is caused by pelvic pathology (e.g. endometriosis, adenomyosis and fibroids). It is important to differentiate between these two types of dysmenorrhoea to enable appropriate management.

Women with bleeding disorders commonly experience dysmenorrhoea. This could be explained by the increased prevalence of menorrhagia amongst them. The severity of dysmenorrhoea and its interference on daily work have been shown to be significantly greater in women with bleeding disorders than the control group [158]; 52% of women with bleeding disorders reported moderate, severe or very severe pain during their period compared with 28% in the controls. In another study, 86% (70/81) of the type I VWD patients reported menstrual pain rated at median score of 4 on a scale of 1–10 [162].

Non-steroidal anti-inflammatory drugs are commonly used and effective in the treatment of dysmenorrhoea. Their use, however, is contraindicated in women with bleeding disorders because of the anti-platelet aggregating effect, making the management of dysmenorrhoea in these women difficult. Other treatment options include other types of analgesia (such as paracetamol and codeine), oral contraceptives and surgery in the presence of pelvic pathology.

Miscarriages Several case reports and case series have documented a significant risk of miscarriage and placental abruption resulting in fetal loss or premature delivery among women with FXIII deficiency [239–241] and congenital afibrinogenemia [242–244].

Whether women with other bleeding disorders have an increased risk of miscarriage is unclear. Miscarriage is common in the general population, with 12–13.5% of recognized pregnancies resulting in spontaneous miscarriage [245,246]. When women were followed with serial serum human chorionic gonadotrophin measurements, a high miscarriage rate of 31% was found [247]. In two series of women with VWD [54,62], the reported prevalence of miscarriage was 22% and 25% respectively. Another study reported a miscarriage rate of 31% among 72 intended pregnancies in 32 haemophilia carriers [28]. Further studies are needed to confirm whether inherited bleeding disorders, other than deficiency of FXIII or fibrinogen, are associated with a higher rate of miscarriage.

Factor replacement has been used to reduce the probability of miscarriage in women with deficiency of FXIII and fibrinogen [240,248,249]. However, there is currently no evidence for its role in women with other bleeding disorders.

Other gynaecological problems In the survey of 102 women with VWD, a higher prevalence of endometrial hyperplasia (10% vs. 1%), endometrial polyps (8% vs. 1%) and fibroids (32% vs. 17%) were reported amongst women with VWD compared with controls [250]. As these conditions can manifest with bleeding symptoms, it is likely that more women with bleeding disorders become symptomatic. However, there is currently insufficient evidence to suggest that these conditions are more prevalent amongst women with bleeding disorders and further studies are required in this area.

Women with inherited bleeding disorders are more likely to be symptomatic from gynaecological problems that are associated with bleeding. Awareness of an underlying bleeding disorder will allow appropriate management. A multidisciplinary approach is essential in the management of women with inherited bleeding disorders (grade C, level IV).

References

- Gill JC. The role of genetics in inhibitor formation. *Thromb Haemost* 1999; **82**: 500–504.
- Ludlam CA, Pasi KJ, Bolton-Maggs P *et al*. A framework for genetic service provision for haemophilia and other inherited bleeding disorders. *Haemophilia* 2005; **11**: 145–163.
- McIntyre L. Pre-implantation diagnosis. *STEER: Succinct Timely Eval Evid Rev* 2001; **1**: 1–9.
- Michaelides K, Tuddenham EG, Turner C, Lavelle B, Lavery SA. Live birth following the first mutation specific pre-implantation genetic diagnosis for haemophilia A. *Thromb Haemost* 2006; **95**: 373–379.
- Human Fertilisation and Embryology Authority. *HFEA Guide to Infertility and Directory of Clinics 2005/06*. London: Human Fertilisation and Embryology Authority, 2006.
- Department of Health UK. *Preimplantation Genetic Diagnosis (PGD) – Guiding Principles for Commissioners of NHS Services*. UK: Department of Health UK, 2002.
- Thornhill AR, de Die-Smulders CE, Geraedts JP *et al*. ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)'. *Hum Reprod* 2005; **20**: 35–48.
- Firth HV, Boyd PA, Chamberlain PF, MacKenzie IZ, Morriss-Kay GM, Huson SM. Analysis of limb reduction defects in babies exposed to chorionic villus sampling. *Lancet* 1994; **343**: 1069–1071.
- Nicolaides K, Brizot ML, Patel F, Snijders R. Comparison of chorionic villus sampling and amniocentesis for fetal karyotyping at 10–13 weeks' gestation. *Lancet* 1994; **344**: 435–439.
- Tabor A, Philip J, Madsen M, Bang J, Obel EB, Norgaard-Pedersen B. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. *Lancet* 1986; **1**: 1287–1293.
- Wilson RD, Farquharson DF, Wittmann BK, Shaw D. Cordocentesis: overall pregnancy loss rate as important as procedure loss rate. *Fetal Diagn Ther* 1994; **9**: 142–148.
- Forestier F, Daffos F, Rainaut M, Sole Y, Amiral J. Vitamin K dependent proteins in fetal hemostasis at mid trimester of pregnancy. *Thromb Haemost* 1985; **53**: 401–403.
- Forestier F, Daffos F, Galacteros F, Bardakjian J, Rainaut M, Beuzard Y. Hematological values of 163 normal fetuses between 18 and 30 weeks of gestation. *Pediatr Res* 1986; **20**: 342–346.
- Royal College of Obstetricians and Gynaecologists. *Amniocentesis and Chorionic Villus Sampling*. Guideline No. 8. London: RCOG Press, 2005.
- Stephens JD, Sherman S. Determination of fetal sex by ultrasound. *N Engl J Med* 1983; **309**: 984.
- Plattner G, Renner W, Went J, Beaudette L, Viau G. Fetal sex determination by ultrasound scan in the second and third trimesters. *Obstet Gynecol* 1983; **61**: 454–458.
- Birnholz JC. Determination of fetal sex. *N Engl J Med* 1983; **309**: 942–944.
- Natsuyama E. Sonographic determination of fetal sex from twelve weeks of gestation. *Am J Obstet Gynecol* 1984; **149**: 748–757.
- Elejalde BR, de Elejalde MM, Heitman T. Visualization of the fetal genitalia by ultrasonography: a review of the literature and analysis of its accuracy and ethical implications. *J Ultrasound Med* 1985; **4**: 633–639.
- Ammini AC, Sabherwal U, Mukhopadhyay C, Vijayaraghavan M, Pandey J. Morphogenesis of the human external male genitalia. *Pediatr Surg Int* 1997; **12**: 401–406.
- Whitlow BJ, Lazanakis MS, Economides DL. The sonographic identification of fetal gender from 11 to 14 weeks of gestation. *Ultrasound Obstet Gynecol* 1999; **13**: 301–304.
- Efrat Z, Akinfenwa OO, Nicolaides KH. First-trimester determination of fetal gender by ultrasound. *Ultrasound Obstet Gynecol* 1999; **13**: 305–307.
- Costa JM, Benachi A, Gautier E, Jouannic JM, Ernault P, Dumez Y. First-trimester fetal sex determination in maternal serum using real-time PCR. *Prenat Diagn* 2001; **21**: 1070–1074.

- 24 Honda H, Miharu N, Ohashi Y *et al.* Fetal gender determination in early pregnancy through qualitative and quantitative analysis of fetal DNA in maternal serum. *Hum Genet* 2002; **110**: 75–79.
- 25 Hromadnikova I, Houbova B, Hridelova D *et al.* Replicate real-time PCR testing of DNA in maternal plasma increases the sensitivity of non-invasive fetal sex determination. *Prenat Diagn* 2003; **23**: 235–238.
- 26 Chi C, Hyett JA, Finning KM, Lee CA, Kadir RA. Non-invasive first trimester determination of fetal gender: a new approach for prenatal diagnosis of haemophilia. *BJOG* 2006; **113**: 239–242.
- 27 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**: 909–918.
- 28 Kadir RA, Economides DL, Braithwaite J, Goldman E, Lee CA. The obstetric experience of carriers of haemophilia. *Br J Obstet Gynaecol* 1997; **104**: 803–810.
- 29 United Kingdom Haemophilia Centre Doctors' Organisation. Guidelines on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia* 2003; **9**: 1–23.
- 30 Mannucci PM. The choice of plasma-derived clotting factor concentrates. *Baillieres Clin Haematol* 1996; **9**: 273–290.
- 31 Mannucci PM, Gdovin S, Gringeri A *et al.* Transmission of hepatitis A to patients with hemophilia by factor VIII concentrates treated with organic solvent and detergent to inactivate viruses. The Italian Collaborative Group. *Ann Intern Med* 1994; **120**: 1–7.
- 32 Azzi A, Ciappi S, Zakvrzewska K, Morfini M, Mariani G, Mannucci PM. Human parvovirus B19 infection in hemophiliacs first infused with two high-purity, virally attenuated factor VIII concentrates. *Am J Hematol* 1992; **39**: 228–230.
- 33 Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 1997; **90**: 2515–2521.
- 34 Ray JG. DDAVP use during pregnancy: an analysis of its safety for mother and child. *Obstet Gynecol Surv* 1998; **53**: 450–455.
- 35 Mannucci PM. Use of desmopressin (DDAVP) during early pregnancy in factor VIII-deficient women. *Blood* 2005; **105**: 3382.
- 36 Letsky EA. Haemostasis and epidural anaesthesia. *Int J Obstet Anesth* 1991; **1**: 51–54.
- 37 Abramovitz S, Beilin Y. Thrombocytopenia, low molecular weight heparin, and obstetric anaesthesia. *Anesthesiol Clin North America* 2003; **21**: 99–109.
- 38 Dhar P, Abramovitz S, DiMichele D, Gibb CB, Gadalla F. Management of pregnancy in a patient with severe haemophilia A. *Br J Anaesth* 2003; **91**: 432–435.
- 39 Kulkarni R, Lusher JM, Henry RC, Kallen DJ. Current practices regarding newborn intracranial haemorrhage and obstetrical care and mode of delivery of pregnant haemophilia carriers: a survey of obstetricians, neonatologists and haematologists in the United States, on behalf of the National Hemophilia Foundation's Medical and Scientific Advisory Council. *Haemophilia* 1999; **5**: 410–415.
- 40 Ljung R, Lindgren AC, Petrini P, Tengborn L. Normal vaginal delivery is to be recommended for haemophilia carrier gravidae. *Acta Paediatr* 1994; **83**: 609–611.
- 41 El-Refaey H, Rodeck C. Postpartum haemorrhage: definitions, medical and surgical management. A time for change. *Br Med Bull* 2003; **67**: 205–217.
- 42 Hoveyda F, MacKenzie IZ. Secondary postpartum haemorrhage: incidence, morbidity, and current management. *BJOG* 2001; **108**: 927–930.
- 43 Mauser Bunschoten EP, van Houwelingen JC, Sjamsoedin Visser EJ, van Dijken PJ, Kok AJ, Sixma JJ. Bleeding symptoms in carriers of hemophilia A and B. *Thromb Haemost* 1988; **59**: 349–352.
- 44 Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labour. *Cochrane Database Syst Rev* 2000; CD000007.
- 45 Kulkarni R, Lusher JM. Intracranial and extracranial hemorrhages in newborns with hemophilia: a review of the literature. *J Pediatr Hematol Oncol* 1999; **21**: 289–295.
- 46 Kulkarni R, Lusher J. Perinatal management of newborns with haemophilia. *Br J Haematol* 2001; **112**: 264–274.
- 47 Chalmers EA, Williams MD, Richards M *et al.* Management of neonates with inherited bleeding disorders – a survey of current UK practice. *Haemophilia* 2005; **11**: 186–187.
- 48 Buchanan GR. Factor concentrate prophylaxis for neonates with hemophilia. *J Pediatr Hematol Oncol* 1999; **21**: 254–256.
- 49 Lorenzo JI, Lopez A, Altisent C, Aznar JA. Incidence of factor VIII inhibitors in severe haemophilia: the importance of patient age. *Br J Haematol* 2001; **113**: 600–603.
- 50 van der Bom JG, Mauser-Bunschoten EP, Fischer K, van den Berg HM. Age at first treatment and immune tolerance to factor VIII in severe hemophilia. *Thromb Haemost* 2003; **89**: 475–479.
- 51 Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood* 1987; **69**: 454–459.
- 52 Miller CH. Genetics of hemophilia and von Willebrand's disease. In: Hilgartner MW, ed. *Hemophilia in the Child and Adult*. New York: Masson, 1982: 29–62.
- 53 Punnonen R, Nyman D, Gronroos M, Wallen O. Von Willebrand's disease and pregnancy. *Acta Obstet Gynecol Scand* 1981; **60**: 507–509.
- 54 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**: 314–321.

- 55 Hanna W, McCarroll D, McDonald T *et al.* Variant von Willebrand's disease and pregnancy. *Blood* 1981; **58**: 873–879.
- 56 Conti M, Mari D, Conti E, Muggiasca ML, Mannucci PM. Pregnancy in women with different types of von Willebrand disease. *Obstet Gynecol* 1986; **68**: 282–285.
- 57 Adashi EY. Lack of improvement in von Willebrand's disease during pregnancy. *N Engl J Med* 1980; **303**: 1178.
- 58 Ramsahoye BH, Davies SV, Dasani H, Pearson JF. Obstetric management in von Willebrand's disease: a report of 24 pregnancies and a review of the literature. *Haemophilia* 1995; **1**: 140–144.
- 59 Kujovich JL. von Willebrand disease and pregnancy. *J Thromb Haemost* 2005; **3**: 246–253.
- 60 Rick ME, Williams SB, Sacher RA, McKeown LP. Thrombocytopenia associated with pregnancy in a patient with type IIB von Willebrand's disease. *Blood* 1987; **69**: 786–789.
- 61 Caliezi C, Tsakiris DA, Behringer H, Kuhne T, Marbet GA. Two consecutive pregnancies and deliveries in a patient with von Willebrand's disease type 3. *Haemophilia* 1998; **4**: 845–849.
- 62 Foster PA. The reproductive health of women with von Willebrand Disease unresponsive to DDAVP: results of an international survey. On behalf of the Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the ISTH. *Thromb Haemost* 1995; **74**: 784–790.
- 63 Steer C, Campbell S, Davies M, Mason B, Collins W. Spontaneous abortion rates after natural and assisted conception. *Br Med J* 1989; **299**: 1317–1318.
- 64 Castaman G, Eikenboom JC, Contri A, Rodeghiero F. Pregnancy in women with type 1 von Willebrand disease caused by heterozygosity for von Willebrand factor mutation C1130F. *Thromb Haemost* 2000; **84**: 351–352.
- 65 Ito M, Yoshimura K, Toyoda N, Wada H. Pregnancy and delivery in patients with von Willebrand's disease. *J Obstet Gynaecol Res* 1997; **23**: 37–43.
- 66 Cohen AJ, Kessler CM, Ewenstein BM. Management of von Willebrand disease: a survey on current clinical practice from the haemophilia centres of North America. *Haemophilia* 2001; **7**: 235–241.
- 67 Pasi KJ, Collins PW, Keeling DM *et al.* Management of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2004; **10**: 218–231.
- 68 Walker ID, Walker JJ, Colvin BT, Letsky EA, Rivers R, Stevens R. Investigation and management of haemorrhagic disorders in pregnancy. Haemostasis and Thrombosis Task Force. *J Clin Pathol* 1994; **47**: 100–108.
- 69 Holmberg L, Nilsson IM, Borge L, Gunnarsson M, Sjorin E. Platelet aggregation induced by 1-desamino-8-D-arginine vasopressin (DDAVP) in Type IIB von Willebrand's disease. *N Engl J Med* 1983; **309**: 816–821.
- 70 Dennis MW, Clough V, Toh CH. Unexpected presentation of type 2N von Willebrand disease in pregnancy. *Haemophilia* 2000; **6**: 696–697.
- 71 Walzman M, Bonnar J. Effects of tranexamic acid on the coagulation and fibrinolytic systems in pregnancy complicated by placental bleeding. *Arch Toxicol Suppl* 1982; **5**: 214–220.
- 72 Lindoff C, Rybo G, Astedt B. Treatment with tranexamic acid during pregnancy, and the risk of thrombo-embolic complications. *Thromb Haemost* 1993; **70**: 238–240.
- 73 Svanberg L, Astedt B, Nilsson IM. Abruptio placentae—treatment with the fibrinolytic inhibitor tranexamic acid. *Acta Obstet Gynecol Scand* 1980; **59**: 127–130.
- 74 Gai MY, Wu LF, Su QF, Tatsumoto K. Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-center, randomized trial. *Eur J Obstet Gynecol Reprod Biol* 2004; **112**: 154–157.
- 75 Jones BP, Bell EA, Maroof M. Epidural labor analgesia in a parturient with von Willebrand's disease type IIA and severe preeclampsia. *Anesthesiology* 1999; **90**: 1219–1220.
- 76 Milaskiewicz RM, Holdcroft A, Letsky E. Epidural anaesthesia and von Willebrand's disease. *Anaesthesia* 1990; **45**: 462–464.
- 77 Cohen S, Daitch JS, Amar D, Goldiner PL. Epidural analgesia for labor and delivery in a patient with von Willebrand's disease. *Reg Anesth* 1989; **14**: 95–97.
- 78 Roque H, Funai E, Lockwood CJ. von Willebrand disease and pregnancy. *J Matern Fetal Med* 2000; **9**: 257–266.
- 79 Kulkarni A, Riddell A, Lee CA, Kadir RA. *Assessment of Factor VIII and von Willebrand Factor Levels in Cord Blood*. RCOG 6th International Scientific Meeting, Cairo, Egypt, 2005.
- 80 Rapaport SI, Proctor RR, Patch MJ, Yettra M. The mode of inheritance of PTA deficiency: evidence for the existence of major PTA deficiency and minor PTA deficiency. *Blood* 1961; **18**: 149–165.
- 81 Leiba H, Ramot B, Many A. Heredity and coagulation studies in ten families with Factor XI (plasma thromboplastin antecedent) deficiency. *Br J Haematol* 1965; **11**: 654–665.
- 82 Bolton-Maggs PH, Young Wan-Yin B, McCraw AH, Slack J, Kernoff PB. Inheritance and bleeding in factor XI deficiency. *Br J Haematol* 1988; **69**: 521–528.
- 83 Bolton-Maggs PH, Patterson DA, Wensley RT, Tud-denham EG. Definition of the bleeding tendency in factor XI-deficient kindreds—a clinical and laboratory study. *Thromb Haemost* 1995; **73**: 194–202.
- 84 Ragni MV, Sinha D, Seaman F, Lewis JH, Spero JA, Walsh PN. Comparison of bleeding tendency, factor

- XI coagulant activity, and factor XI antigen in 25 factor XI-deficient kindreds. *Blood* 1985; **65**: 719–724.
- 85 Salomon O, Steinberg DM, Tamarin I, Zivelin A, Seligsohn U. Plasma replacement therapy during labor is not mandatory for women with severe factor XI deficiency. *Blood Coagul Fibrinolysis* 2005; **16**: 37–41.
- 86 Bolton-Maggs PH. The management of factor XI deficiency. *Haemophilia* 1998; **4**: 683–688.
- 87 Condie RG. A serial study of coagulation factors XII, XI and X in plasma in normal pregnancy and in pregnancy complicated by pre-eclampsia. *Br J Obstet Gynaecol* 1976; **83**: 636–639.
- 88 Hilgartner MW, Smith CH. Plasma thromboplastin antecedent (Factor XI) in the neonate. *J Pediatr* 1965; **66**: 747–752.
- 89 Nossel HL, Lanzkowsky P, Levy S, Mibashan RS, Hansen JD. A study of coagulation factor levels in women during labour and in their newborn infants. *Thromb Diath Haemorrh* 1966; **16**: 185–197.
- 90 Mannucci PM, Bauer KA, Santagostino E *et al.* Activation of the coagulation cascade after infusion of a factor XI concentrate in congenitally deficient patients. *Blood* 1994; **84**: 1314–1319.
- 91 Bolton-Maggs PH, Colvin BT, Satchi BT, Lee CA, Lucas GS. Thrombogenic potential of factor XI concentrate. *Lancet* 1994; **344**: 748–749.
- 92 Billon S, Le Niger C, Escoffre-Barbe M, Vicariot M, Abgrall JF. The use of recombinant factor VIIa (NovoSeven) in a patient with a factor XI deficiency and a circulating anticoagulant. *Blood Coagul Fibrinolysis* 2001; **12**: 551–553.
- 93 O'Connell NM. Factor XI deficiency—from molecular genetics to clinical management. *Blood Coagul Fibrinolysis* 2003; **14**(Suppl. 1): S59–S64.
- 94 Bern MM, Sahud M, Zhukov O, Qu K, Mitchell W Jr. Treatment of factor XI inhibitor using recombinant activated factor VIIa. *Haemophilia* 2005; **11**: 20–25.
- 95 Brown SA. What dose of recombinant activated factor VII should be used in patients with factor XI deficiency? *Haemophilia* 2005; **11**: 430–431.
- 96 Bolton-Maggs PH, Perry DJ, Chalmers EA *et al.* The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. *Haemophilia* 2004; **10**: 593–628.
- 97 David AL, Paterson-Brown S, Letsky EA. Factor XI deficiency presenting in pregnancy: diagnosis and management. *BJOG* 2002; **109**: 840–843.
- 98 Bolton-Maggs PH, Wensley RT, Kernoff PB *et al.* Production and therapeutic use of a factor XI concentrate from plasma. *Thromb Haemost* 1992; **67**: 314–319.
- 99 Peyvandi F, Duga S, Akhavan S, Mannucci PM. Rare coagulation deficiencies. *Haemophilia* 2002; **8**: 308–321.
- 100 Oehler MK, Rees MC. Menorrhagia: an update. *Acta Obstet Gynecol Scand* 2003; **82**: 405–422.
- 101 Royal College of Obstetricians and Gynaecologists. *The Initial Management of Menorrhagia – National Evidence-based Clinical Guidelines*. London: RCOG Press, 1998.
- 102 Hallberg L, Hogdahl AM, Nilsson L, Rybo G. Menstrual blood loss – a population study. Variation at different ages and attempts to define normality. *Acta Obstet Gynecol Scand* 1966; **45**: 320–351.
- 103 Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol* 1990; **97**: 734–739.
- 104 Reid PC, Coker A, Coltart R. Assessment of menstrual blood loss using a pictorial chart: a validation study. *BJOG* 2000; **107**: 320–322.
- 105 Rees MC. Role of menstrual blood loss measurements in management of complaints of excessive menstrual bleeding. *Br J Obstet Gynaecol* 1991; **98**: 327–328.
- 106 Royal College of Obstetricians and Gynaecologists. *The Management of Menorrhagia in Secondary Care – National Evidence-based Clinical Guidelines*. London: RCOG Press, 1999.
- 107 Warner P, Critchley HO, Lumsden MA, Campbell-Brown M, Douglas A, Murray G. Referral for menstrual problems: cross sectional survey of symptoms, reasons for referral, and management. *Br Med J* 2001; **323**: 24–28.
- 108 Rees M. Menorrhagia. *Br Med J (Clin Res Ed)* 1987; **294**: 759–762.
- 109 Clarke A, Black N, Rowe P, Mott S, Howle K. Indications for and outcome of total abdominal hysterectomy for benign disease: a prospective cohort study. *Br J Obstet Gynaecol* 1995; **102**: 611–620.
- 110 Chi C, Shiltagh N, Kingman CEC, Economides DL, Lee CA, Kadir RA. Identification and management of women with inherited bleeding disorder: A survey of obstetrician and gynaecologists in the United Kingdom. *Haemophilia* 2006; **12**: 405–412.
- 111 Dilley A, Drews C, Lally C, Austin H, Barnhart E, Evatt B. A survey of gynecologists concerning menorrhagia: perceptions of bleeding disorders as a possible cause. *J Womens Health Gend Based Med* 2002; **11**: 39–44.
- 112 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**: 893–898.
- 113 Shankar M, Lee CA, Sabin CA, Economides DL, Kadir RA. Willebrand disease in women with menorrhagia: a systematic review. *BJOG* 2004; **111**: 734–740.
- 114 Dilley A, Drews C, Miller C *et al.* Willebrand disease and other inherited bleeding disorders in women with diagnosed menorrhagia. *Obstet Gynecol* 2001; **97**: 630–636.

- 115 Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. *Lancet* 1998; **351**: 485–489.
- 116 Edlund M, Blomback M, von Schoultz B, Andersson O. On the value of menorrhagia as a predictor for coagulation disorders. *Am J Hematol* 1996; **53**: 234–238.
- 117 Philipp CS, Dilley A, Miller CH *et al.* Platelet functional defects in women with unexplained menorrhagia. *J Thromb Haemost* 2003; **1**: 477–484.
- 118 Neinstein LS. Menstrual problems in adolescents. *Med Clin North Am* 1990; **74**: 1181–1203.
- 119 Caufriez A. Menstrual disorders in adolescence: pathophysiology and treatment. *Horm Res* 1991; **36**: 156–159.
- 120 Falcone T, Desjardins C, Bourque J, Granger L, Hemmings R, Quiros E. Dysfunctional uterine bleeding in adolescents. *J Reprod Med* 1994; **39**: 761–764.
- 121 Bevan JA, Maloney KW, Hillery CA, Gill JC, Montgomery RR, Scott JP. Bleeding disorders: a common cause of menorrhagia in adolescents. *J Pediatr* 2001; **138**: 856–861.
- 122 Kadir RA, Lee CA. Menorrhagia in adolescents. *Pediatr Ann* 2001; **30**: 541–546.
- 123 Oral E, Cagdas A, Gezer A, Kaleli S, Aydin Y, Ocer F. Hematological abnormalities in adolescent menorrhagia. *Arch Gynecol Obstet* 2002; **266**: 72–74.
- 124 Jayasinghe Y, Moore P, Donath S, Campbell J, Monagle P, Grover S. Bleeding disorders in teenagers presenting with menorrhagia. *Aust N Z J Obstet Gynaecol* 2005; **45**: 439–443.
- 125 Claessens EA, Cowell CA. Acute adolescent menorrhagia. *Am J Obstet Gynecol* 1981; **139**: 277–280.
- 126 Smith YR, Quint EH, Hertzberg RB. Menorrhagia in adolescents requiring hospitalization. *J Pediatr Adolesc Gynecol* 1998; **11**: 13–15.
- 127 Philipp CS, Faiz A, Dowling N *et al.* Age and the prevalence of bleeding disorders in women with menorrhagia. *Obstet Gynecol* 2005; **105**: 61–66.
- 128 Conlan MG, Folsom AR, Finch A *et al.* Associations of factor VIII and von Willebrand factor with age, race, sex, and risk factors for atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) Study. *Thromb Haemost* 1993; **70**: 380–385.
- 129 Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Variations in coagulation factors in women: effects of age, ethnicity, menstrual cycle and combined oral contraceptive. *Thromb Haemost* 1999; **82**: 1456–1461.
- 130 Kouides PA, Conard J, Peyvandi F, Lukes A, Kadir R. Hemostasis and menstruation: appropriate investigation for underlying disorders of hemostasis in women with excessive menstrual bleeding. *Fertil Steril* 2005; **84**: 1345–1351.
- 131 Kadir RA, Lukes AS, Kouides PA, Fernandez H, Goudemand J. Management of excessive menstrual bleeding in women with hemostatic disorders. *Fertil Steril* 2005; **84**: 1352–1359.
- 132 Fricke W, Kouides P, Kessler C *et al.* A multicenter clinical evaluation of the Clot Signature Analyzer. *J Thromb Haemost* 2004; **2**: 763–768.
- 133 Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. *Blood* 2004; **104**: 1243–1252.
- 134 Federici AB. The factor VIII/von Willebrand factor complex: basic and clinical issues. *Haematologica* 2003; **88**: EREP02.
- 135 Laffan M, Brown SA, Collins PW *et al.* The diagnosis of von Willebrand disease: a guideline from the UK Haemophilia Centre Doctors' Organization. *Haemophilia* 2004; **10**: 199–217.
- 136 Sadler JE, Mannucci PM, Berntorp E *et al.* Impact, diagnosis and treatment of von Willebrand disease. *Thromb Haemost* 2000; **84**: 160–174.
- 137 Abildgaard CF, Suzuki Z, Harrison J, Jefcoat K, Zimmerman TS. Serial studies in von Willebrand's disease: variability versus 'variants'. *Blood* 1980; **56**: 712–716.
- 138 Blomback M, Eneroth P, Andersson O, Anvret M. On laboratory problems in diagnosing mild von Willebrand's disease. *Am J Hematol* 1992; **40**: 117–120.
- 139 Mandalaki T, Louizou C, Dimitriadou C, Symeonidis P. Variations in factor VIII during the menstrual cycle in normal women. *N Engl J Med* 1980; **302**: 1093–1094.
- 140 Kouides P, Phatak P, Sham RL *et al.* Adjusting the reference range of von Willebrand factor levels and factor VIII:C levels in relation to the menstrual cycle. *Blood* 1997; **90**: 32a.
- 141 Onundarson PT, Gudmundsdottir BR, Arnfinnsdottir AV, Kjeld M, Olafsson O. Von Willebrand factor does not vary during normal menstrual cycle. *Thromb Haemost* 2001; **85**: 183–184.
- 142 Miller CH, Dilley AB, Drews C, Richardson L, Evatt B. Changes in von Willebrand factor and factor VIII levels during the menstrual cycle. *Thromb Haemost* 2002; **87**: 1082–1083.
- 143 Alperin JB. Estrogens and surgery in women with von Willebrand's disease. *Am J Med* 1982; **73**: 367–371.
- 144 Mangal AK, Naiman SC. Oral contraceptives and von Willebrand's disease. *Can Med Assoc J* 1983; **128**: 1274.
- 145 Beller FK, Ebert C. Effects of oral contraceptives on blood coagulation. A review. *Obstet Gynecol Surv* 1985; **40**: 425–436.
- 146 Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ Jr, Montgomery RR. The effect of ABO blood group on the diagnosis of von Willebrand disease. *Blood* 1987; **69**: 1691–1695.
- 147 Nitu-Whalley IC, Lee CA, Griffioen A, Jenkins PV, Pasi KJ. Type 1 von Willebrand disease – a clinical retrospective study of the diagnosis, the influence of the ABO blood group and the role of the bleeding history. *Br J Haematol* 2000; **108**: 259–264.
- 148 Philipp CS, Miller CH, Faiz A *et al.* Screening women with menorrhagia for underlying bleeding

- disorders: the utility of the platelet function analyser and bleeding time. *Haemophilia* 2005; **11**: 497–503.
- 149 Posan E, McBane RD, Grill DE, Motsko CL, Nichols WL. Comparison of PFA-100 testing and bleeding time for detecting platelet hypofunction and von Willebrand disease in clinical practice. *Thromb Haemost* 2003; **90**: 483–490.
- 150 Quiroga T, Goycoolea M, Munoz B *et al.* Template bleeding time and PFA-100 have low sensitivity to screen patients with hereditary mucocutaneous hemorrhages: comparative study in 148 patients. *J Thromb Haemost* 2004; **2**: 892–898.
- 151 Scott JC, Mussey E. Menstrual patterns in myxoedema. *Am J Obstet Gynecol* 1964; **90**: 161–165.
- 152 Wilansky DL, Greisman B. Early hypothyroidism in patients with menorrhagia. *Am J Obstet Gynecol* 1989; **160**: 673–677.
- 153 Blum M, Blum G. The possible relationship between menorrhagia and occult hypothyroidism in IUD-wearing women. *Adv Contracept* 1992; **8**: 313–317.
- 154 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**: 40–48.
- 155 Ragni MV, Bontempo FA, Hassett AC. von Willebrand disease and bleeding in women. *Haemophilia* 1999; **5**: 313–317.
- 156 Hayward CP. Inherited platelet disorders. *Curr Opin Hematol* 2003; **10**: 362–368.
- 157 James AH. More than menorrhagia: a review of the obstetric and gynaecological manifestations of bleeding disorders. *Haemophilia* 2005; **11**: 295–307.
- 158 Kadir RA, Sabin CA, Pollard D, Lee CA, Economides DL. Quality of life during menstruation in patients with inherited bleeding disorders. *Haemophilia* 1998; **4**: 836–841.
- 159 Kristjansdottir J, Johansson ED, Ruusuvaara L. The cost of the menstrual cycle in young Swedish women. *Eur J Contracept Reprod Health Care* 2000; **5**: 152–156.
- 160 Kirtava A, Crudder S, Dilley A, Lally C, Evatt B. 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**: 158–161.
- 161 Khan A, Pollard D, Lee CA, Kadir RA. A first year clinical review of the multidisciplinary haemophilia/obstetrics and gynaecology clinic at the Royal Free Hospital Haemophilia Centre. *Haemophilia* 2004; **10**(Suppl. 3): 143–145.
- 162 Kouides PA, Phatak PD, Burkart P *et al.* Gynaecological and obstetrical morbidity in women with type I von Willebrand disease: results of a patient survey. *Haemophilia* 2000; **6**: 643–648.
- 163 Dockeray CJ, Sheppard BL, Daly L, Bonnar J. The fibrinolytic enzyme system in normal menstruation and excessive uterine bleeding and the effect of tranexamic acid. *Eur J Obstet Gynecol Reprod Biol* 1987; **24**: 309–318.
- 164 Gleeson NC. Cyclic changes in endometrial tissue plasminogen activator and plasminogen activator inhibitor type 1 in women with normal menstruation and essential menorrhagia. *Am J Obstet Gynecol* 1994; **171**: 178–183.
- 165 Wellington K, Wagstaff AJ. Tranexamic acid: a review of its use in the management of menorrhagia. *Drugs* 2003; **63**: 1417–1433.
- 166 Gleeson NC, Buggy F, Sheppard BL, Bonnar J. The effect of tranexamic acid on measured menstrual loss and endometrial fibrinolytic enzymes in dysfunctional uterine bleeding. *Acta Obstet Gynecol Scand* 1994; **73**: 274–277.
- 167 Callender ST, Warner GT, Cope E. Treatment of menorrhagia with tranexamic acid. A double-blind trial. *Br Med J* 1970; **4**: 214–216.
- 168 Milsom I, Andersson K, Andersch B, Rybo G. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Am J Obstet Gynecol* 1991; **164**: 879–883.
- 169 Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. *Br J Obstet Gynaecol* 1995; **102**: 401–406.
- 170 Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. *Br Med J* 1996; **313**: 579–582.
- 171 Lethaby A, Farquhar C, Cooke I. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2000; CD000249.
- 172 Rybo G. Tranexamic acid therapy: effective treatment in heavy menstrual bleeding: clinical update on safety. *Therapeutic Adv* 1991; **4**: 1–8.
- 173 British Medical Association and the Royal Pharmaceutical Society of Great Britain. *British National Formulary*. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2004.
- 174 Ong YL, Hull DR, Mayne EE. Menorrhagia in von Willebrand disease successfully treated with single daily dose tranexamic acid. *Haemophilia* 1998; **4**: 63–65.
- 175 Callard GV, Litofsky FS, DeMerre LJ. Menstruation in women with normal or artificially controlled cycles. *Fertil Steril* 1966; **17**: 684–688.
- 176 Ramcharan S, Pellegrin FA, Ray RM, Hsu JP. The Walnut Creek Contraceptive Drug Study. A prospective study of the side effects of oral contraceptives. Volume III, an interim report: a comparison of disease occurrence leading to hospitalization or death in users and nonusers of oral contraceptives. *J Reprod Med* 1980; **25**: 345–372.

- 177 Nilsson L, Rybo G. Treatment of menorrhagia. *Am J Obstet Gynecol* 1971; **110**: 713–720.
- 178 Fraser IS, McCarron G. Randomized trial of 2 hormonal and 2 prostaglandin-inhibiting agents in women with a complaint of menorrhagia. *Aust N Z J Obstet Gynaecol* 1991; **31**: 66–70.
- 179 Vercellini P, De Giorgi O, Mosconi P, Stellato G, Vicentini S, Crosignani PG. Cyproterone acetate versus a continuous monophasic oral contraceptive in the treatment of recurrent pelvic pain after conservative surgery for symptomatic endometriosis. *Fertil Steril* 2002; **77**: 52–61.
- 180 Sulak PJ, Cressman BE, Waldrop E, Holleman S, Kuehl TJ. Extending the duration of active oral contraceptive pills to manage hormone withdrawal symptoms. *Obstet Gynecol* 1997; **89**: 179–183.
- 181 Sulak PJ, Scow RD, Preece C, Riggs MW, Kuehl TJ. Hormone withdrawal symptoms in oral contraceptive users. *Obstet Gynecol* 2000; **95**: 261–266.
- 182 Kwiecien M, Edelman A, Nichols MD, Jensen JT. Bleeding patterns and patient acceptability of standard or continuous dosing regimens of a low-dose oral contraceptive: a randomized trial. *Contraception* 2003; **67**: 9–13.
- 183 Miller L, Notter KM. Menstrual reduction with extended use of combination oral contraceptive pills: randomized controlled trial. *Obstet Gynecol* 2001; **98**: 771–778.
- 184 Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. *Obstet Gynecol* 2003; **101**: 653–661.
- 185 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 Syst Rev* 2005; CD004695.
- 186 Lethagen S, Harris AS, Sjorin E, Nilsson IM. Intranasal and intravenous administration of desmopressin: effect on F VIII/vWF, pharmacokinetics and reproducibility. *Thromb Haemost* 1987; **58**: 1033–1036.
- 187 Cash JD, Gader AM, da Costa J. Proceedings: the release of plasminogen activator and factor VIII to lysine vasopressin, arginine vasopressin, 1-desamino-8-d-arginine vasopressin, angiotensin and oxytocin in man. *Br J Haematol* 1974; **27**: 363–364.
- 188 Mannucci PM, Aberg M, Nilsson IM, Robertson B. Mechanism of plasminogen activator and factor VIII increase after vasoactive drugs. *Br J Haematol* 1975; **30**: 81–93.
- 189 Sakariassen KS, Cattaneo M, vd Berg A, Ruggeri ZM, Mannucci PM, Sixma JJ. DDAVP enhances platelet adherence and platelet aggregate growth on human artery subendothelium. *Blood* 1984; **64**: 229–236.
- 190 Mannucci PM, Canciani MT, Rota L, Donovan BS. Response of factor VIII/von Willebrand factor to DDAVP in healthy subjects and patients with haemophilia A and von Willebrand's disease. *Br J Haematol* 1981; **47**: 283–293.
- 191 Mannucci PM, Vicente V, Alberca I *et al.* Intravenous and subcutaneous administration of desmopressin (DDAVP) to hemophiliacs: pharmacokinetics and factor VIII responses. *Thromb Haemost* 1987; **58**: 1037–1039.
- 192 Rose EH, Aledort LM. Nasal spray desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease. *Ann Intern Med* 1991; **114**: 563–568.
- 193 Lethagen S, Ragnarson TG. Self-treatment with desmopressin intranasal spray in patients with bleeding disorders: effect on bleeding symptoms and socio-economic factors. *Ann Hematol* 1993; **66**: 257–260.
- 194 Lethagen S, Harris AS, Nilsson IM. Intranasal desmopressin (DDAVP) by spray in mild hemophilia A and von Willebrand's disease type I. *Blut* 1990; **60**: 187–191.
- 195 Edlund M, Blomback M, He S. On the correlation between local fibrinolytic activity in menstrual fluid and total blood loss during menstruation and effects of desmopressin. *Blood Coagul Fibrinolysis* 2003; **14**: 593–598.
- 196 Bonnar J, Sheppard BL, Dockeray CJ. The haemostatic system and dysfunctional uterine bleeding. *Res Clin Forum* 1983; **5**: 27–36.
- 197 Rodeghiero F, Castaman G, Mannucci PM. Prospective multicenter study on subcutaneous concentrated desmopressin for home treatment of patients with von Willebrand disease and mild or moderate hemophilia A. *Thromb Haemost* 1996; **76**: 692–696.
- 198 Leissinger C, Becton D, Cornell C Jr, Cox GJ. High-dose DDAVP intranasal spray (Stimate) for the prevention and treatment of bleeding in patients with mild haemophilia A, mild or moderate type 1 von Willebrand disease and symptomatic carriers of haemophilia A. *Haemophilia* 2001; **7**: 258–266.
- 199 Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL. DDAVP nasal spray for treatment of menorrhagia in women with inherited bleeding disorders: a randomized placebo-controlled crossover study. *Haemophilia* 2002; **8**: 787–793.
- 200 Edlund M, Blomback 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**: 225–231.
- 201 Janssen CA, Scholten PC, Heintz AP. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. *Obstet Gynecol* 1995; **85**: 977–982.
- 202 Coulter A, Kelland J, Peto V, Rees MC. Treating menorrhagia in primary care. An overview of drug trials and a survey of prescribing practice. *Int J Technol Assess Health Care* 1995; **11**: 456–471.
- 203 Lethaby A, Irvine G, Cameron I. Cyclical progestogens for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2000; CD001016.

- 204 Irvine GA, Campbell-Brown MB, Lumsden MA, Heikkila A, Walker JJ, Cameron IT. Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia. *Br J Obstet Gynaecol* 1998; **105**: 592–598.
- 205 Lethaby A, Augood C, Duckitt K. Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2000; CD000400.
- 206 Silverberg SG, Haukkamaa M, Arko H, Nilsson CG, Luukkainen T. Endometrial morphology during long-term use of levonorgestrel-releasing intrauterine devices. *Int J Gynecol Pathol* 1986; **5**: 235–241.
- 207 Stewart A, Cummins C, Gold L, Jordan R, Phillips W. The effectiveness of the levonorgestrel-releasing intrauterine system in menorrhagia: a systematic review. *BJOG* 2001; **108**: 74–86.
- 208 Lethaby AE, Cooke I, Rees M. Progesterone/progestogen releasing intrauterine systems versus either placebo or any other medication for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2000; CD002126.
- 209 Reid PC, Virtanen-Kari S. Randomised comparative trial of the levonorgestrel intrauterine system and mefenamic acid for the treatment of idiopathic menorrhagia: a multiple analysis using total menstrual fluid loss, menstrual blood loss and pictorial blood loss assessment charts. *BJOG* 2005; **112**: 1121–1125.
- 210 Lahteenmaki P, Haukkamaa M, Puolakka J *et al.* Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. *Br Med J* 1998; **316**: 1122–1126.
- 211 Hurskainen R, Teperi J, Rissanen P *et al.* Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial. *Lancet* 2001; **357**: 273–277.
- 212 Hurskainen R, Teperi J, Rissanen P *et al.* Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow-up. *JAMA* 2004; **291**: 1456–1463.
- 213 Hidalgo M, Bahamondes L, Perrotti M, Diaz J, Dantas-Monteiro C, Petta C. Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years. *Contraception* 2002; **65**: 129–132.
- 214 Andersson K, Od lind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. *Contraception* 1994; **49**: 56–72.
- 215 Sivin I, el Mahgoub S, McCarthy T *et al.* Long-term contraception with the levonorgestrel 20 mcg day⁻¹ (LNg 20) and the copper T 380Ag intrauterine devices: a five-year randomized study. *Contraception* 1990; **42**: 361–378.
- 216 Nagrani R, Bowen-Simpkins P, Barrington JW. Can the levonorgestrel intrauterine system replace surgical treatment for the management of menorrhagia? *BJOG* 2002; **109**: 345–347.
- 217 Xiao B, Wu SC, Chong J, Zeng T, Han LH, Luukkainen T. Therapeutic effects of the levonorgestrel-releasing intrauterine system in the treatment of idiopathic menorrhagia. *Fertil Steril* 2003; **79**: 963–969.
- 218 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**: 1425–1428.
- 219 Lukes AS, Kouides PA. Hysterectomy versus expanded medical treatment for abnormal uterine bleeding: clinical outcomes in the medicine or surgery trial. *Obstet Gynecol* 2004; **104**: 864–865.
- 220 Maresh MJ, Metcalfe MA, McPherson K *et al.* The VALUE national hysterectomy study: description of the patients and their surgery. *BJOG* 2002; **109**: 302–312.
- 221 McPherson K, Metcalfe MA, Herbert A *et al.* Severe complications of hysterectomy: the VALUE study. *BJOG* 2004; **111**: 688–694.
- 222 Lethaby A, Shepperd S, Cooke I, Farquhar C. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2000; CD000329.
- 223 Lethaby A, Hickey M. Endometrial destruction techniques for heavy menstrual bleeding: a Cochrane review. *Hum Reprod* 2002; **17**: 2795–2806.
- 224 Toth D, Gervaise A, Kuzel D, Fernandez H. Thermal balloon ablation in patients with multiple morbidity: 3-year follow-up. *J Am Assoc Gynecol Laparosc* 2004; **11**: 236–239.
- 225 Rubin G, Wortman M, Kouides PA. Endometrial ablation for von Willebrand disease-related menorrhagia – experience with seven cases. *Haemophilia* 2004; **10**: 477–482.
- 226 Silwer J. von Willebrand's disease in Sweden. *Acta Paediatr Scand Suppl* 1973; **238**: 1–159.
- 227 Hann LE, Hall DA, Black EB, Ferrucci JT Jr. Mittelschmerz. Sonographic demonstration. *JAMA* 1979; **241**: 2731–2732.
- 228 O'Brien PM, DiMichele DM, Walterhouse DO. Management of an acute hemorrhagic ovarian cyst in a female patient with hemophilia A. *J Pediatr Hematol Oncol* 1996; **18**: 233–236.
- 229 Jarvis RR, Olsen ME. Type I von Willebrand's disease presenting as recurrent corpus hemorrhagicum. *Obstet Gynecol* 2002; **99**: 887–888.
- 230 Mishell DR Jr. Noncontraceptive health benefits of oral steroidal contraceptives. *Am J Obstet Gynecol* 1982; **142**: 809–816.
- 231 Bottini E, Pareti FI, Mari D, Mannucci PM, Muggiasca ML, Conti M. Prevention of hemoperitoneum during ovulation by oral contraceptives in women with type III von Willebrand disease and afibrinogenemia.

- genemia. Case reports. *Haematologica* 1991; 76: 431–433.
- 232 Ghosh K, Mohanty D, Pathare AV, Jijina F. Recurrent haemoperitoneum in a female patient with type III von Willebrand's disease responded to administration of oral contraceptive. *Haemophilia* 1998; 4: 767–768.
- 233 Vercellini P, De Giorgi O, Aimi G, Panazza S, Uglietti A, Crosignani PG. Menstrual characteristics in women with and without endometriosis. *Obstet Gynecol* 1997; 90: 264–268.
- 234 D'Hooghe TM, Bambra CS, Raeymaekers BM, Koninckx PR. Increased prevalence and recurrence of retrograde menstruation in baboons with spontaneous endometriosis. *Hum Reprod* 1996; 11: 2022–2025.
- 235 Klein JR, Litt IF. Epidemiology of adolescent dysmenorrhea. *Pediatrics* 1981; 68: 661–664.
- 236 Campbell MA, McGrath PJ. Use of medication by adolescents for the management of menstrual discomfort. *Arch Pediatr Adolesc Med* 1997; 151: 905–913.
- 237 Davis AR, Westhoff CL. Primary dysmenorrhea in adolescent girls and treatment with oral contraceptives. *J Pediatr Adolesc Gynecol* 2001; 14: 3–8.
- 238 Banikarim C, Chacko MR, Kelder SH. Prevalence and impact of dysmenorrhea on Hispanic female adolescents. *Arch Pediatr Adolesc Med* 2000; 154: 1226–1229.
- 239 Burrows RF, Ray JG, Burrows EA. Bleeding risk and reproductive capacity among patients with factor XIII deficiency: a case presentation and review of the literature. *Obstet Gynecol Surv* 2000; 55: 103–108.
- 240 Rodeghiero F, Castaman GC, Di Bona E, Ruggeri M, Dini E. Successful pregnancy in a woman with congenital factor XIII deficiency treated with substitutive therapy. Report of a second case. *Blut* 1987; 55: 45–48.
- 241 Inbal A, Muszbek L. Coagulation factor deficiencies and pregnancy loss. *Semin Thromb Hemost* 2003; 29: 171–174.
- 242 Kobayashi T, Kanayama N, Tokunaga N, Asahina T, Terao T. Prenatal and peripartum management of congenital afibrinogenemia. *Br J Haematol* 2000; 109: 364–366.
- 243 Evron S, Anteby SO, Brzezinsky A, Samueloff A, Eldor A. Congenital afibrinogenemia and recurrent early abortion: a case report. *Eur J Obstet Gynecol Reprod Biol* 1985; 19: 307–311.
- 244 Grech H, Majumdar G, Lawrie AS, Savidge GF. Pregnancy in congenital afibrinogenemia: report of a successful case and review of the literature. *Br J Haematol* 1991; 78: 571–572.
- 245 Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. *Br Med J* 1997; 315: 32–34.
- 246 Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *Br Med J* 2000; 320: 1708–1712.
- 247 Wilcox AJ, Weinberg CR, O'Connor JF *et al.* Incidence of early loss of pregnancy. *N Engl J Med* 1988; 319: 189–194.
- 248 Trehan AK, Fergusson IL. Congenital afibrinogenemia and successful pregnancy outcome. Case report. *Br J Obstet Gynaecol* 1991; 98: 722–724.
- 249 Kobayashi T, Asahina T, Maehara K, Itoh M, Kanayama N, Terao T. Congenital afibrinogenemia with successful delivery. *Gynecol Obstet Invest* 1996; 42: 66–69.
- 250 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: 292–297.

Appendix 1

The definitions of types of evidence used in this guideline originate from the US Agency for Health Care Policy and Research. Where possible, recommendations are based on the evidence that supports them.

Classification of evidence levels

- Ia Evidence obtained from meta-analysis of randomized controlled trials.
- Ib Evidence obtained from at least one randomized controlled trial.
- IIa Evidence obtained from at least one well-designed controlled study without randomization.
- IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.
- III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
- IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendation

- A. Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia and Ib).
- B. Requires the availability of well-documented clinical studies but no randomized clinical trials on the topic of recommendation (evidence levels IIa, IIb and III).

C. Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV).







Appendix 2

Pictorial blood assessment chart and scoring system for the assessment of menstrual blood loss.

Name:

LMP:

Score:

TOWEL	1	2	3	4	5	6	7	8
								
								
								
CLOT FLOODING								
TAMPON	1	2	3	4	5	6	7	8
								
								
								
CLOT FLOODING								

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 clot (size of 1p coin)
5 Points	For large clot (size of 50p coin)

From Higham *et al.* [103], with permission.

Summary of recommendations

A. Pregnancy in carriers of haemophilia

1. Pre-pregnancy counselling should be offered to carriers of haemophilia to discuss suitable reproductive options and methods of prenatal diagnosis (grade C, level IV).

2. Pregnancy in carriers of haemophilia should be managed by a multidisciplinary team including an obstetrician, haematologist and anaesthetist (grade C, level IV).

3. Chorionic villus sampling is the method of choice for specific prenatal diagnosis of haemophilia. Maternal clotting factor level should be checked prior to any invasive procedures and prophylactic treatment arranged if the level is <50 IU dL^{-1} (grade C, level IV).

4. Knowledge of fetal gender allows invasive testing to be avoided in female pregnancies and enables appropriate management of labour and delivery; therefore, the importance of establishing fetal sex in pregnancies at risk of haemophilia should be conveyed to the parents (grade C, level IV).

5. Carriers of haemophilia should have their clotting factor level (FVIII or FIX) checked at booking and at 28 and 34 weeks of gestation to allow appropriate management of labour and delivery and to assess the need for prophylactic treatment (grade C, level IV).

6. Recombinant FVIII and FIX should be used as the treatment of choice in pregnant carriers of haemophilia A and B (grade C, level IV).

7. A delivery plan should be made in advance and for women carrying an affected fetus, delivery should be planned at a unit where the necessary expertise in the management of this disorder and resources for laboratory testing and clotting factor treatments are readily available (grade C, level IV).

8. Regional block in carriers of haemophilia is not contraindicated if the coagulation screen is normal and the relevant factor level is above 50 IU dL^{-1} (or raised to >50 IU dL^{-1} by prophylactic treatment). It should be performed by an expert anaesthetist with the help of a specialised haematologist for assessment of coagulation status and arrangement of treatment if required (grade C, level IV).

9. The use of fetal scalp electrodes and fetal blood sampling should be avoided in affected male fetuses or when fetal sex or coagulation status of male fetus is unknown (grade C, level IV).

10. Vacuum extraction, mid-cavity forceps and prolonged labour should be avoided in affected male fetuses or when fetal sex or coagulation status of male fetus is unknown. Delivery should be achieved by the least traumatic method and early recourse to caesarean section should be considered (grade C, level IV).

11. Active management of third stage should be practised in carriers of haemophilia (grade C, level IV).

12. Factor levels should be monitored postdelivery and maintained above 50 IU dL^{-1} for at least 3 days, or 5 days if caesarean section has been performed (grade C, level IV).

13. Intramuscular injections and venepunctures should be avoided in neonates affected by haemophilia or whose coagulation status is unknown. Vitamin K should be given orally and routine immunizations should be given intradermally or subcutaneously. Circumcision should be delayed until the coagulation status of the neonate is known

and appropriate management can be arranged by the haematologist (grade C, level IV).

14. Cord blood should be collected from all male offspring of carriers of haemophilia to assess clotting factor levels for identification and early management of newborns at risk. The results of the tests should be conveyed to the parents by an appropriate member of the haemophilia team (grade C, level IV).

15. Cranial ultrasound/CT scans should be arranged for all neonates with haemophilia if labour had been premature, traumatic, e.g. following forceps delivery or prolonged labour, or if there are any clinical signs suggestive of bleeding. In these cases it is recommended that recombinant clotting factor should be administered to raise the plasma clotting factor to 100 IU dL⁻¹ (grade C, level IV).

B. Pregnancy in women with VWD

1. Prenatal diagnosis is not required in the majority of families with VWD, but should be discussed and offered to women at risk of having a child with type 3 VWD (grade C, level IV).

2. Pregnancy in women with VWD should be managed by a multidisciplinary team including an obstetrician, haematologist and anaesthetist (grade C, level IV).

3. Factor levels including VWF:Ag, VWF:AC and FVIII:C should be checked at booking, 28 and 34 weeks and prior to invasive procedures. Prophylactic treatment should be given when factor levels are <50 IU dL⁻¹ to cover invasive procedures and delivery (grade C, level IV).

4. DDAVP can be used in pregnancy, but repeated administration or use in pregnancies complicated with pre-eclampsia must be avoided. Close monitoring for water retention must accompany its use (grade C, level IV).

5. Women with type I VWD generally do not require prophylactic treatment for delivery. In type 2 VWD, treatment is required for operative delivery or if there is perineal trauma. Women with type 3 VWD require treatment for all types of delivery (grade C, level IV).

6. A delivery plan should be made in advance. For women with severe VWD, delivery should be planned at a unit where the necessary expertise in the management of this disorder and resources for laboratory testing and clotting factor treatments are readily available (grade C, level IV).

7. Epidural anaesthesia can be offered for use in majority of women with type 1 VWD whose VWF:AC is >50 IU dL⁻¹ (or raised to >50 IU dL⁻¹ by prophylactic treatment). It should be carried out

by an experienced anaesthetist. It is not recommended for use in type 2 or 3 VWD (group C, level IV).

8. Women with VWF:AC <50 IU dL⁻¹ should receive prophylactic treatment at the onset of labour or prior to planned caesarean section (grade C, level IV).

9. Active management of third stage should be practised in women with VWD (grade C, level IV).

10. Factor levels should be monitored post-delivery and prophylaxis given to maintain von Willebrand factor activity and factor VIII levels >50 IU dL⁻¹ for at least 3 days, or 5 days following caesarean section. Tranexamic acid or combined oral contraceptive pill should be considered to control prolonged and/or intermittent secondary PPH (grade C, level IV).

11. For fetuses at risk of type 2, type 3 or moderately severe type 1 VWD, invasive monitoring techniques, vacuum extraction and rotational/mid-cavity forceps should be avoided and a cord blood sample should be sent for assessment (grade C, level IV).

12. Intramuscular injections and venepunctures should be avoided in neonates whose coagulation status is unknown. Vitamin K should be given orally and routine immunizations should be given intradermally or subcutaneously. Circumcision should be delayed until the coagulation status of the neonate is known and appropriate management can be arranged by the haematologist (grade C, level IV).

C. Pregnancy in women with FXI deficiency

1. Pregnancy in women with FXI deficiency requires specialised and individualized care provided collaboratively by an obstetrician, haematologist and anaesthetist (grade C, level IV).

2. Due to the unpredictability of the condition, attempts should be made to identify the individual's clinical bleeding tendency and the coexistence of confounding factors (grade C, level IV).

3. Prenatal diagnosis should be discussed and offered to patients where there is a risk of severe factor XI deficiency (grade C, level IV).

4. Factor XI levels should be checked at booking, 28 and 34 weeks and prior to invasive procedures. Many patients can be managed expectantly but patients with severely low levels or a positive bleeding history should be given prophylaxis to cover invasive procedures (grade C, level IV).

5. A delivery plan should be made in advance. It is recommended for women with FXI deficiency to deliver at a unit where the necessary expertise in the management of this disorder and resources for

laboratory testing and clotting factor treatments are readily available (grade C, level IV).

6. Women with severe deficiency and/or a bleeding history, should receive prophylactic treatment at the onset of labour or prior to planned induction or caesarean section. Where prophylaxis has been given, it should be extended to 3 days postpartum or 5 days following caesarean section (grade C, level IV).

7. Active management of third stage should be practised in women with FXI deficiency (grade C, level IV).

8. Care should be taken to avoid unnecessary trauma to the baby at delivery and a umbilical cord blood sample for FXI level should be obtained (grade C, level IV).

D. Menorrhagia in women inherited bleeding disorders

1. The use of PBAC should be considered in the assessment of menstrual blood loss for the diagnosis of menorrhagia and evaluation of the treatment outcomes (grade C, level IV).

2. A significant proportion of women with idiopathic menorrhagia have an underlying bleeding disorder, the commonest being VWD. Therefore testing for these disorders should be considered (grade B, level III).

3. Adolescents presenting with acute menorrhagia should be investigated for bleeding disorders. For prepubertal girls either known to have a bleeding disorder or a positive family history, plans should be made in anticipation of the possibility of acute menorrhagia at the onset of menarche (grade C, level IV).

4. Initial investigation for an underlying bleeding disorder in women with menorrhagia should consist of a focus personal and family history of bleeding symptoms (grade C, level IV).

5. Laboratory testing for an inherited bleeding disorder should be carried out if the woman presenting with menorrhagia has a positive bleeding history or if surgical intervention is planned (grade C, level IV).

6. Laboratory testing should only be undertaken in settings where necessary expertise and resources are available on-site to ensure appropriate and accurate diagnosis (grade C, level IV).

7. Laboratory testing should be carried out in the following stepwise sequence (grade C, level IV):

1 FBC and Ferritin;

2 PT and APTT;

3 Von Willebrand screen (VWF:Ag, VWF:RCO, FVIII:C). Testing exclusively during menstruation, off COC, or adjusted for blood type is not necessary at the initial evaluation. However, these details should be documented and repeat testing should be considered if the results are borderline.

4 Platelet function analysis (platelet aggregation and release studies);

5 Other clotting factor levels;

6 Thyroid function tests if symptomatic.

8. Menorrhagia is one of the most common bleeding manifestations in women with inherited bleeding disorders and has a negative effect on their quality of life (grade B, level III).

9. Management of menorrhagia in women with inherited bleeding disorders should be provided by a multidisciplinary team including a haematologist and gynaecologist (grade C, level IV).

10. Medical treatment of menorrhagia in women with inherited bleeding disorders include tranexamic acid, combined oral contraceptives, DDAVP, cyclical 21-days oral progesterone, and the LNG-IUS. The treatment choice depends on the type of bleeding disorder, and patient's age, childbearing status and preferences in terms of the perceived efficacy and side effects (grade C, level IV).

11. Specific haemostatic therapy will be required in some women with inherited bleeding disorders to control menorrhagia. A multidisciplinary approach in the management of these individuals is essential to ensure optimal outcomes (grade C, level IV).

12. Prophylactic treatment should be considered in women with inherited bleeding disorders undergoing surgery for treatment of menorrhagia. The surgery should be performed by experienced professionals with special attention to haemostasis. The use of a surgical drain should be considered (grade C, level IV).

13. Women with inherited bleeding disorders are more likely to be symptomatic from gynaecological problems that are associated with bleeding. Awareness of an underlying bleeding disorder will allow appropriate management. A multidisciplinary approach is essential in the management of women with inherited bleeding disorders (grade C, level IV).