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Management of Inherited Bleeding Disorders in Pregnancy

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Management of Inherited Bleeding Disorders in Pregnancy

This is the first edition of a combined United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) and Royal College of Obstetricians and Gynaecologists (RCOG) guideline although a previous guideline was written by the UKHCDO in 2006.

Executive summary of recommendations

Haemophilia

What is the definition?

Clinicians should be aware that haemophilia is an X-linked condition associated with reduction or absence of clotting factor VIII (haemophilia A) or IX (haemophilia B), causing bleeding symptoms. ✓

How should inheritance be assessed?

Up to 50% of neonatal males with severe haemophilia have no previous family history. In these cases, there is a 90% chance that the mother is a carrier, with risk to the next male child. D

A family tree should be constructed to assess the likelihood of haemophilia carriership in at-risk female family members. ✓

Females at risk of carrying haemophilia, particularly severe haemophilia, should be tested for the genetic mutation present in affected family members, if available. ✓

What are the different phenotypes and how is severity assessed?

Clinicians should be aware of the different phenotypes and severities of haemophilia, as this influences risk and required management. ✓

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What are the risks in pregnancy to mother and baby?

Known or potential female carriers may have low factor VIII/IX levels. The levels should be checked prior to an invasive procedure or in association with bleeding symptoms. D

Clinicians should be aware that carriers of haemophilia are at increased risk of bleeding with invasive procedures, termination, spontaneous miscarriage and at the time of delivery. D

Male neonates with haemophilia are at increased risk of bleeding, including intracranial haemorrhage (ICH) and extracranial haemorrhage (ECH). C

Male neonates with haemophilia are at risk of iatrogenic bleeding following delivery. ✓

What is the prepregnancy management?

The baseline factor level should be determined prior to onset of pregnancy. ✓

Before pregnancy, the general health of women who are carriers for haemophilia should be optimised, including attention to weight and correction of any iron deficiency. ✓

How should genetic counselling be provided?

Genetic counselling should be provided to women at risk, ideally before pregnancy, by appropriately qualified and experienced clinical staff. ✓

Written informed consent should be obtained in advance of any genetic testing. ✓

What are the options for prenatal diagnosis (PND)?

Carriers of severe haemophilia should be offered preimplantation genetic diagnosis. ✓

Carriers of severe haemophilia with a male fetus confirmed to be affected by haemophilia should be counselled to enable informed choices. D

All carriers of severe haemophilia should be offered fetal sex determination by free fetal DNA analysis from 9 weeks of gestation. D

Pregnant carriers of severe haemophilia with a male fetus at risk of haemophilia should be offered the option of PND with chorionic villus sampling at 11–14 weeks of gestation. ✓

All carriers of haemophilia with male fetuses should be offered third trimester amniocentesis if diagnostic investigations have not previously been performed to determine haemophilia status to inform options for delivery. ✓

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What is the antepartum management?

Antenatal care should be delivered in the context of a multidisciplinary team setting with haematologists and obstetricians with expertise in this field. ✓

Maternal factor VIII/IX should be checked at booking, before any antenatal procedure and in the third trimester; factor VIII levels rise in pregnancy, but factor IX tends to remain stable. D

Aim for factor VIII/IX levels of at least 0.5 iu/ml to cover surgical or invasive procedures, or spontaneous miscarriage. If treatment is required, factor levels of 1.0 iu/ml should be aimed for and not allowed to fall below 0.5 iu/ml until haemostasis is secure. C

Tranexamic acid should be considered in combination with treatment for all those with levels of less than 0.5 iu/ml or as sole therapy for those with levels above 0.5 iu/ml if clinically indicated. Following miscarriage, it should be continued until the bleeding settles. D

Desmopressin (DDAVP) can be used antenatally to raise factor VIII levels. Due to the antidiuretic effect, fluids should be restricted to 1 litre for 24 hours after use or, if not possible, electrolytes should be monitored. C

Recombinant factor VIII should be used if levels obtained with DDAVP are insufficient or in a known nonresponder. C

Recombinant factor IX is required to cover invasive or surgical procedures in women with factor levels less than 0.5 iu/ml. ✓

When giving treatment to raise clotting factor levels, it is important to monitor the response to treatment by measuring the plasma clotting factor concentration before and after infusion, and 4–6 hours following treatment to facilitate dosing. ✓

Following any invasive or surgical procedure, a plan for ongoing treatment is required to maintain the coagulation factor in the normal range for a suitable duration, determined by the nature of the procedure. ✓

A clear plan for the intrapartum care of a carrier and the baby should be available in advance of 37 weeks of gestation. The woman should be seen in the anaesthetic clinic and the neonatologists should be informed of the intended delivery of a baby with haemophilia. ✓

If antenatal diagnosis has not been performed in a male fetus, then he should be managed as if he is affected. ✓

External cephalic version should be avoided in affected or potentially affected male fetuses and female fetuses who are obligate or possible carriers of severe haemophilia B. ✓

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What is the optimal mode and timing of delivery?

A decision regarding the timing and mode of delivery should be agreed jointly between the woman and the multidisciplinary team. C

The option of a planned lower segment caesarean section should be discussed for the delivery of affected male babies, especially those with severe haemophilia and/or if the fetal status is unknown. However, there needs to be a full assessment of the advantages and disadvantages of this mode of delivery and consideration of obstetric factors, maternal bleeding risk, patient preference and reproductive expectations. D

If elective caesarean section is intended, this should be at 39^{+0} completed weeks with a clear plan for the event of spontaneous labour occurring beforehand. D

For intended vaginal delivery, spontaneous labour is preferred, if no other obstetric concerns, to minimise the risk of intervention. Measures should be taken to ensure expertise and necessary resources are available at all times. Planned induction of labour may be necessary in cases where there are concerns about distance of travel to the specialist centre or if there are other obstetric concerns. D

The use of ventouse and midcavity forceps should be avoided for male babies at risk of haemophilia. B

Fetal blood sampling (FBS) and fetal scalp electrode (FSE) should be avoided in babies expected to have severe or moderate haemophilia. In babies potentially affected with mild haemophilia, judicious use of FBS and FSE can be considered, in order to facilitate vaginal delivery and avoid morbidity associated with caesarean section in labour. This decision should be made by a senior obstetrician. Where FBS is used, sustained pressure under direct vision should be used to ensure haemostasis. ✓

The plan for intrapartum management and the second stage of labour, involving a senior obstetrician, should be documented. ✓

There is no evidence to recommend special measures for delivery in women carrying female fetuses. A female fetus who is at risk of carrying severe haemophilia B may theoretically be more at risk of ICH/ECH and this should be considered in the birth plan. ✓

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How can analgesia and anaesthesia be managed safely?

Factor VIII/IX levels of more than 0.5 iu/ml are required for the insertion and removal of epidural catheter and for spinal anaesthesia. D

Experienced clinicians should be involved in decisions about whether or not to perform a central neuraxial anaesthetic technique, and the woman should be given all the information she needs to make an informed choice. ✓

The most suitable form of analgesia depends on the context of the delivery. All carriers should have the opportunity to discuss analgesia with a senior anaesthetist prior to delivery. A clear plan for analgesia and anaesthesia should be available in the maternal records. D

Intramuscular injections should generally be avoided if factor VIII/IX levels are less than 0.5 iu/ml. They may be used when a woman's factor VIII/IX is maintained in the normal range by clotting factor support or DDAVP. ✓

What is the haemostatic management during labour?

If clotting factor levels are less than 0.5 iu/ml, DDAVP should be given to raise factor VIII, or factor IX concentrate should be given to raise factor IX, aiming for 1.0 iu/ml. ✓

Tranexamic acid could be considered as sole therapy for women with low normal levels or in conjunction with DDAVP to increase factor VIII, or with substantive factor IX treatment. ✓

Treatment should be given as close to delivery as possible. ✓

What is the postpartum management?

To minimise the risk of postpartum haemorrhage (PPH), it is important to recommend/offer active management of the third stage of labour. ✓

Levels of factor VIII/IX should be maintained above 0.5 iu/ml for at least 3 days following an uncomplicated vaginal delivery or 5 days following instrumental delivery or caesarean section. Management should be guided by results of factor assays. D

Tranexamic acid should be continued postpartum until lochia is minimal. B

Pharmacological thromboprophylaxis should generally be avoided where the factor level is 0.6 iu/ml or less, but will need to be considered in women with thrombotic risk factors, with careful balance of risks. ✓

Following discharge from hospital, the haemophilia centre should maintain contact with the woman who should be advised to report any increase in postpartum blood loss. ✓

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What is the neonatal management?

A plan for diagnostic testing of the neonate following delivery, including cord blood sampling, should be included in the maternal pregnancy management plan. ✓

Coagulation results in neonates should be interpreted against age-adjusted reference ranges. D

Cord blood sampling and diagnostic testing is recommended for all male babies born to mothers who are carriers of haemophilia A/B although some mild cases may require retesting at 3–6 months of age. D

Cord blood sampling and diagnostic testing of female babies born to mothers who are carriers of haemophilia is not recommended. D

Parents of neonates diagnosed with haemophilia should be informed of the diagnosis in a timely manner and arrangements should be made for neonatal follow-up at a haemophilia centre. ✓

In a neonate with low factor levels, vitamin K should be administered by an oral regimen and following neonate bloodspot screening, pressure should be sustained to avoid excess bleeding. ✓

Cranial ultrasound (US) should be considered prior to discharge in all neonates with severe or moderate haemophilia. ✓

Cranial magnetic resonance imaging (MRI) should be undertaken in neonates with symptoms or signs suggestive of ICH even in the presence of a normal cranial US. D

In neonates with haemophilia, information on the symptoms and signs of ICH should be provided at the time of discharge. ✓

Short-term primary prophylaxis should be considered in severe and moderate haemophilia in infants considered to be at increased risk of bleeding due to trauma at delivery or prematurity. D

Clinical bleeding events in neonates with haemophilia should be managed in accordance with treatment guidelines. D

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von Willebrand disease (VWD)

What is the classification and inheritance?

VWD is classified according to whether the deficiency of von Willebrand factor (VWF) is partial quantitative (type 1), qualitative (type 2) or severe quantitative (type 3). The classification is important for diagnosis, treatment and counselling of patients. However, it does not reliably predict response to therapy and has a variable association with VWF gene mutations. B

Clinicians counselling these women should be aware that inheritance of VWD is autosomal and variably dominant or recessive, depending on the VWD type. ✓

Genetic counselling about the risk of disease transmission, and its variable penetrance and expression, should be provided for all women with VWD. ✓

What are the risks in pregnancy to mother and baby?

Clinicians should be aware that women with VWD have an increased risk of antepartum, primary and secondary PPH. B

All women should receive counselling about risks of increased bleeding, especially women with type I VWD whose VWF level does not rise above 0.5 iu/ml by term, or type 2 or 3 VWD. B

What is the prepregnancy and antenatal management?

Prior to conception, the bleeding phenotype should be assessed, historical diagnosis reviewed and response to DDAVP established. D

Safe management requires a multidisciplinary approach. ✓

All women with VWD should have VWF antigen levels and activity, and factor VIII levels checked at booking, in the third trimester and prior to any invasive procedures. ✓

Women with type 1 VWD who achieve normal VWF levels can be safely managed in standard obstetric units in collaboration with haemophilia centre staff. ✓

Women with types 2 and 3, or severe type 1 VWD should be referred for prenatal care and delivery to a centre where there are specialists in high-risk obstetrics, as well as a haemophilia centre. Facilities for laboratory monitoring of VWF and factor VIII levels are essential. D

Clinicians should aim for factor VIII and VWF ristocetin cofactor (VWF:RCo) activity levels of 0.5 iu/ml or above to cover surgical procedures or spontaneous miscarriage. ✓

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Where invasive procedures are required, if VWF activity or factor VIII levels are less than 0.50 iu/ml, women should receive haemostatic support in the form of DDAVP, where responsive, or VWF-containing concentrates. ✓

Treatment should be with DDAVP in preference to blood-derived factor concentrates where possible. This is safe for use in pregnancy and at delivery, but should be avoided in pre-eclampsia. D

Fluid intake should be restricted to 1 litre for 24 hours following DDAVP administration to prevent maternal hyponatraemia. If additional fluid is required, electrolytes should be monitored. D

Clinicians should be aware that patients with type 2B VWD may develop thrombocytopenia following DDAVP treatment. D

If VWF replacement therapy is required, a concentrate containing factor VIII and VWF, manufactured from a safe plasma source with adequate viral testing and inactivation procedures should be used. ✓

Target peak VWF activity levels should be 1.0 iu/ml and levels maintained above 0.5 iu/ml until haemostasis is secured. ✓

For most antenatal procedures, a single preoperative treatment is sufficient, but in some cases, a second dose may be required at 12–24 hours, depending on the nature of the procedure and the measured levels. ✓

What is the intrapartum management?

The timing of treatment should be as near to delivery as possible, and pre- and post-treatment levels of VWF activity and factor VIII levels should be measured and repeated after delivery, or if labour is prolonged. ✓

Tranexamic acid should be considered in combination with treatment for all those with VWF activity less than 0.5 iu/ml, or as sole therapy for those with levels above 0.5 iu/ml if clinically indicated. This can be given orally or intravenously, and can be started prior to delivery. ✓

Platelet transfusions, as well as VWF factor replacement, may sometimes be required in type 2B VWD. D

The mode of delivery should be guided by obstetric indications. Spontaneous labour and normal vaginal delivery should be permitted if there are no other obstetric concerns, to minimise risk of intervention. ✓

For fetuses at risk of having type 2 or 3 VWD, FBS, external cephalic version, fetal scalp monitoring, ventouse delivery and midcavity forceps should be avoided. ✓

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How can analgesia and anaesthesia be safely managed?

For patients with type 1 VWD, where VWF activity has been normalised by pregnancy or treatment, central neuraxial anaesthesia can be offered. ✓

For patients with type 2 disease, central neuraxial anaesthesia should be avoided unless VWF activity is more than 0.5 iu/ml and the haemostatic defect has been corrected; this may be difficult to achieve in type 2 and central neuraxial anaesthesia should not be given in cases of type 3. ✓

For patients with type 2N VWD, central neuraxial anaesthesia should be avoided unless factor VIII level is more than 0.5 iu/ml. ✓

Prior to delivery, all women should be given the opportunity to discuss analgesia with a senior obstetric anaesthetist. ✓

In patients where an epidural catheter has been placed, consideration should be given to the need for repeat treatment prior to catheter removal, as the risk of bleeding is no less than with insertion. D

Intramuscular injections and postnatal nonsteroidal anti-inflammatory drugs (NSAIDs) are only suitable in the short term when VWF activity and factor VIII are more than 0.5 iu/ml. ✓

What is the postpartum management?

It is important to ensure that VWF activity and factor VIII levels are maintained at more than 0.5 iu/ml for at least 3 days following uncomplicated vaginal delivery and at least 5 days following instrumental delivery or after caesarean section. Management should be guided by results of laboratory investigations. ✓

Women with VWD should be considered for tranexamic acid for the postpartum period. A standard dose is 1 g three to four times a day for 7–14 days. In some cases, prolonged administration for 2–3 weeks or more may be necessary. ✓

If thromboprophylaxis is indicated, low-molecular-weight heparin (LMWH) may be given to inpatients with adequate correction of VWF:RCo and factor VIII levels. When pharmacological thromboprophylaxis is contraindicated, mechanical methods should be employed. ✓

Women with VWD should be made aware of the risk of delayed bleeding and be encouraged to report excessive bleeding. For women with more severe cases, haemoglobin should be monitored and regular contact with the patient maintained for several weeks. Patients with type 3 VWD may require treatment with VWF concentrate for 2–3 weeks or even longer following delivery. ✓

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What is the neonatal management?

A plan for the diagnostic testing of the neonate following delivery, including cord blood sampling, should be included in the maternal pregnancy management plan. ✓

Cord blood samples for VWF activity should be taken for babies at risk of type 2 and 3 VWD. ✓

For neonates at risk of type 2 or 3 VWD, vitamin K should be given orally, unless VWF activity is shown to be normal. D

Neonates with type 3 VWD should be considered for routine cranial imaging prior to discharge and for short-term prophylaxis, with factor concentrate, if there has been significant potential trauma at delivery. D

Factor XI deficiency

What is the inheritance?

Factor XI deficiency is an uncommon autosomal disorder which has both recessive and dominant inheritance patterns. B

The incidence in the non-Jewish population is 1/1 000 000; it is common in Ashkenazi Jews with heterozygosity in 8% and homozygosity in 0.2–0.5%. A

Clinicians should be aware that there is intra- and inter-individual variation in bleeding phenotype. D

What are the different phenotypes?

Plasma levels of factor XI show poor correlation with bleeding symptoms. B

Spontaneous bleeding is rare, even with very low factor XI levels. However, these patients are often at risk of bleeding following surgery or trauma. C

Heterozygotes have mild or moderate reduction in factor XI levels (more than 0.15–0.20 iu/ml). Most are asymptomatic, but patients with even mild reductions in factor XI (0.5–0.7 iu/ml) may have a bleeding tendency. C

What are the risks in pregnancy to mother and baby?

Factor XI does not usually increase during pregnancy; however, levels should be checked at booking, in the third trimester and prior to invasive procedures. C

Women with factor XI deficiency may suffer excessive bleeding after miscarriage or termination, especially if they have a bleeding phenotype. C

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There is increased risk of PPH in factor XI-deficient women, which is highest in those with a bleeding phenotype and of blood group O, and least in non-O blood groups with a nonbleeding phenotype. C

Patients with factor XI deficiency should be assessed for the presence of other potentially compounding factors, such as low VWF levels and platelet dysfunction. C

No special precautions for the baby are required for delivery unless the neonate is at risk of homozygosity or compound heterozygosity. D

What are the therapeutic options?

Treatment options include tranexamic acid, factor XI concentrate and fresh frozen plasma (FFP), however, women with a nonbleeding phenotype or unknown status can often be managed expectantly. C

Tranexamic acid should not be given simultaneously with prophylactic factor XI concentrate as this is considered to increase thrombotic risk. For many women, it is likely that tranexamic acid alone will be sufficient to prevent PPH. D

If FFP is given to raise factor XI levels, solvent detergent (SD)-FFP should be used when available. D

Recombinant factor VIIa is not licensed for this condition and is generally not recommended, except if there is an inhibitor to factor XI. D

What is the antenatal, intrapartum and postpartum management?

Factor XI or tranexamic acid is not usually required antenatally unless an invasive procedure is undertaken or if there is bleeding following miscarriage or surgical procedure. C

Delivery plans need to be individualised. Prophylactic factor XI replacement should be considered if homozygous/compound heterozygous, previous history of PPH or general bleeding history. Otherwise, management can be expectant, with tranexamic acid alone and factor replacement reserved for excess bleeding. C

Can central neuraxial anaesthesia be given?

Central neuraxial anaesthesia should not be given to women with low factor XI levels with a known bleeding phenotype, where the phenotype is not clear or when there is a severe reduction in level. In those with a nonbleeding phenotype, discussion and counselling should be given regarding the risks and benefits of allowing neuraxial anaesthesia with or without factor replacement. ✓

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Rare bleeding disorders

What are they?

Clinicians should be aware that rare bleeding disorders include inherited deficiencies of fibrinogen, factors II, V, VII, X, XI and XIII, combined factor V and factor VIII (factor V+VIII) deficiencies, and congenital deficiency of vitamin K-dependent factors. D

What is the inheritance of factors II, V, VII, X and XIII, and combined factor V+VIII deficiencies?

Genetic counselling should be provided, with the understanding that most rare inherited bleeding disorders are autosomal recessive in inheritance and heterozygote carriers are usually asymptomatic. For affected women or asymptomatic heterozygous carriers, consanguinity should be established to allow counselling, screening when possible and formulation of a delivery plan for a potentially affected baby. D

What are the risks in pregnancy to mother and baby, and what are the treatment options?

Clinicians should appreciate that coagulation factor levels can change during pregnancy. However, this is unlikely to influence haemostasis in women with severe deficiency. Management should take into account both the factor level and whether there is a clinical history of bleeding. C

Treatment plans may need to be modified according to the nature of individual bleeds or procedures, and to the background bleeding phenotype of each case. Factor replacement therapy is usually advised for delivery in women with severe coagulation factor deficiency and/or a bleeding history. Tranexamic acid at a dose of 15–20 mg/kg or 1 g four times daily alone can be used for minor bleeds and in combination with factor replacement. D

If the baby is at risk of severe deficiency, the delivery plan should include avoidance of ventouse, midcavity forceps, FBS and FSE. ✓

Central neuraxial anaesthesia, postpartum pharmacological thromboprophylaxis and NSAIDs should usually be avoided in women with severe deficiencies as it may be difficult to guarantee consistent normalisation of haemostasis even after treatment. They may be used after individual assessment if adequate replacement therapy is confirmed. ✓

Prothrombin (factor II) deficiency

If factor II activity is less than 0.2 iu/ml and there is significant bleeding, established labour or prior to caesarean section, give prothrombin complex concentrate 20–40 iu/kg to achieve factor II activity 0.2–0.4 iu/ml. Consider further prothrombin complex concentrate 10–20 iu/kg at 48-hour intervals to maintain factor II activity more than 0.2 iu/ml for at least 3 days. Women already receiving prophylactic prothrombin complex concentrate can continue it throughout pregnancy. D

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Factor V deficiency

For significant bleeding or delivery in women with factor V activity less than 0.2 iu/ml, 15–25 ml/kg FFP should be considered once in established labour or before caesarean section to achieve factor V activity 0.2–0.4 iu/ml with further FFP 10 ml/kg at 12-hour intervals to maintain factor V activity more than 0.2 iu/ml for at least 3 days. Where possible, SD-FFP should be used to reduce infective risk. D

For severe bleeding or caesarean section, consider additional platelet transfusion. D

Severe factor VII deficiency

For factor VII activity less than 0.2 iu/ml in the third trimester with prior history of bleeding, consider recombinant factor VIIa 15–30 micrograms/kg every 4–6 hours for at least 3 or 5 days following caesarean section. For all other women, recombinant factor VIIa 15–30 micrograms/kg is recommended only in response to abnormal bleeding. For mild bleeding, tranexamic acid (15–20 mg/kg or 1 g four times daily) can be used. For severe bleeding, recombinant factor VIIa 15–30 micrograms/kg can be given and repeated if required every 4–6 hours, usually for a minimum of three doses. D

Severe factor X deficiency

For delivery in women with factor X activity less than 0.3 iu/ml in the third trimester who have a history of bleeding and all those who require caesarean section, use prothrombin complex concentrate 20–40 iu/kg (or factor X concentrate if available) to achieve factor X activity more than 0.4 iu/ml. Consider further prothrombin complex concentrate 10–20 iu/kg once daily to maintain factor X activity more than 0.3 iu/ml for at least 3 days. Antenatal prophylaxis may be considered in women with a history of recurrent bleeding or adverse pregnancy outcome using prothrombin complex concentrate 20–30 iu/kg two or three times a week to maintain trough factor X more than 0.01 iu/ml. D

Severe factor XIII deficiency

During pregnancy, increased intensity prophylaxis is required using factor XIII plasma concentrate or recombinant factor XIII (if A-subunit deficiency). Dosing frequency should be increased from every 28 days to every 14–21 days to maintain factor XIII more than 0.2 iu/ml. For delivery, consider additional factor XIII concentrate 10–40 iu/kg once in established labour or before caesarean section, depending on the interval since last prophylaxis. D

Factor V+VIII deficiency

For delivery in women with combined factor V+VIII deficiency, if factor V activity less than 0.2 iu/ml in the third trimester, consider SD-FFP 15–25 ml/kg once in established labour or before caesarean section to achieve factor V activity 0.2–0.4 iu/ml. Consider further SD-FFP 10 ml/kg once every 12 hours to maintain factor V activity more than 0.2 iu/ml for at least 3 days. Consider additional recombinant factor VIII if the factor VIII activity is less than 0.5 iu/ml in the third trimester. D

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Fibrinogen disorders

What is the nature and inheritance of afibrinogenaemia, hypofibrinogenaemia and dysfibrinogenaemia?

Clinicians should be aware that fibrinogen disorders can be autosomal recessive (afibrinogenaemia) or autosomal dominant (with quantitative and/or qualitative defects) and are associated with a variable clinical phenotype. D

What are the risks in pregnancy to mother and baby?

Clinicians should be aware that severe fibrinogen deficiency may be associated with bleeding, but quantitative and qualitative deficiency can also be associated with thrombosis and pregnancy loss. D

What is the management of pregnancy and delivery?

If functional fibrinogen less than 0.5 g/litre, consider prophylaxis throughout pregnancy with fibrinogen concentrate initially 50–100 mg/kg twice per week, adjusted to maintain trough fibrinogen activity more than 1 g/litre. Higher doses of fibrinogen concentrate are likely to be required to maintain fibrinogen activity as pregnancy progresses. Consider additional fibrinogen concentrate for established labour to ensure fibrinogen activity more than 1.5 g/litre for at least 3 days. Tranexamic acid can be used for minor bleeding. D

Because of the variable clinical phenotype associated with hypofibrinogenaemia and dysfibrinogenaemia, a personal and/or family history is required for management decisions. If there is no personal or family history of bleeding or thrombosis, expectant management is recommended for pregnant women or the neonate. D

Fibrinogen replacement therapy is associated with a high risk of thrombosis and requires vigilance. Pregnant women with a thrombotic phenotype or other risk factors for venous thrombosis, and with a low risk of bleeding, should be considered for thromboprophylaxis with LMWH. ✓

Central neuraxial anaesthesia, NSAIDs and intramuscular injections should generally be avoided for women with severe fibrinogen deficiency, or a personal or family history of bleeding, due to the difficulty in assuring correction with factor concentrate. They may be used after individual assessment if adequate replacement therapy is confirmed. ✓

The use of midcavity forceps, rotational forceps, ventouse, FBS and FSE should be avoided in a baby at risk of fibrinogen deficiency associated with a bleeding phenotype. ✓

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Platelet function disorders

Clinicians should be aware that the spectrum of bleeding in patients with platelet function disorders varies and may first present in pregnancy. D

Women known to have a platelet dysfunction disorder should receive prepregnancy counselling from a multidisciplinary specialist team with expertise in caring for patients with platelet function disorders. ✓

Bernard Soulier Syndrome (BSS)

What is the aetiology?

Clinicians should be aware that BSS is caused by genetic abnormality of an important platelet adhesion receptor (glycoprotein [GP] Ib-IX-V receptor) and is often associated with a severe bleeding phenotype. ✓

What is the inheritance?

BSS is an autosomal recessive disorder. In areas of high consanguinity, it may be prudent to test the father using platelet flow cytometry for GP Ib surface density. ✓

What are the maternal risks?

BSS is associated with significant risk of primary and secondary PPH, and wound haematoma. Management of delivery, therefore, requires careful planning with the multidisciplinary team. A

Peripartum haemostatic management should be guided by assessment of the individual phenotype. D

Patients with a bleeding history should be given a platelet transfusion prophylactically at delivery or before caesarean section, in combination with tranexamic acid. Platelets should be human leucocyte antigen (HLA)-matched where possible to reduce the risk of alloimmunisation and platelet refractoriness. D

Tranexamic acid should be given at the onset of labour and continued regularly through the postpartum period until lochia is minimal. D

DDAVP has variable efficacy and is unlikely to be useful as sole therapy in BSS. D

Central neuraxial anaesthesia should be avoided. ✓

Glanzmann's thrombasthenia (GT)

What is the aetiology?

Clinicians should be aware that GT is a disorder of platelet function with autosomal recessive inheritance and is often associated with severe bleeding tendency. ✓

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What are the maternal risks?

GT is associated with significant risk of intrapartum and PPH, and a careful plan of management is needed for women preparing for labour and delivery. B

HLA-matched platelet transfusions and/or recombinant factor VIIa should be given prophylactically, at delivery, for patients with a history of bleeding. Repeat doses may be required depending on the clinical picture. D

DDAVP has not been shown to be effective in GT and is unlikely to be helpful. ✓

Tranexamic acid should be given from the onset of established labour and continued regularly through the postpartum period until lochia is minimal. ✓

Central neuraxial anaesthesia should be avoided. ✓

What are the risks to the fetus?

Maternal alloimmunisation to paternally-derived fetal platelet antigens (GP IIb/IIIa) may cause fetal thrombocytopenia and risk of ICH and other fetal bleeding. B

If fetal-maternal alloimmunisation does not occur, there is no need to restrict aids to delivery. ✓

What are the treatment options?

Women should be monitored for platelet-specific alloantibodies at booking, and at 28 and 34 weeks of gestation. C

If fetal-maternal alloimmunisation occurs, management should involve a fetal medicine unit with experience of these conditions, and treatment with intravenous immunoglobulin with or without steroids should be considered. D

Amniocentesis with platelet typing may be considered in cases of paternal heterozygosity. ✓

If the baby is at risk of homozygous GT or fetomaternal alloimmune thrombocytopenia, restrictions to delivery should be applied, as for all babies at risk of ICH. This includes avoidance of ventouse, midcavity forceps, FSE and fetal scalp sampling. Depending on risk, an elective caesarean section may be considered. B

Neonatal care of potential alloimmunisation requires a cord platelet count and withholding intramuscular vitamin K until the result is known, or administering it orally. A platelet count below the normal range should be repeated at day 3–5 when the platelet nadir is reached, due to development of the neonatal spleen. Platelet transfusion should be given if the platelet count is less than 30 $\times$ 10^9/litre. D

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Other congenital platelet function defects

What are the therapeutic options?

Women with mild platelet function disorders may require treatment to cover delivery. ✓

DDAVP and/or tranexamic acid can be used to cover delivery. D

Tranexamic acid should be continued postpartum until lochia is minimal. ✓

Central neuraxial anaesthesia should only be given if the risks are considered to be outweighed by the benefits and the haemostatic defect has been corrected. A platelet transfusion may be necessary beforehand and epidural catheter should not be left in situ. ✓

1. Purpose and scope

This guideline is intended for both specialist haematologists and obstetricians who have experience in managing pregnant patients with bleeding disorders. In addition, it may be a useful reference text for obstetric anaesthetists and neonatologists.

Women who have inherited bleeding disorders may be at significant risk of bleeding following miscarriage, abortion, antenatal procedures and delivery. They require multidisciplinary specialised care tailored to the individual, with cross-specialty communication, including anaesthetists and neonatologists as necessary. Progress has been made in the identification of obstetric problems in these women and raising clinical awareness among their care providers. Particular aspects of their obstetric management include preconception counselling, prenatal diagnosis (PND), antenatal, intrapartum and postpartum care, and the immediate care for the neonate.

2. Introduction and background epidemiology

The conditions covered in this guideline are haemophilia A and B, von Willebrand disease (VWD), factor XI deficiency, rare factor deficiencies, fibrinogen disorders, Bernard Soulier Syndrome (BSS), Glanzmann's thrombasthenia (GT) and other platelet function disorders.

These conditions vary considerably in the potential impact on mother and baby. Female carriers of haemophilia A and B usually (although not always) have normal levels of factor VIII and IX, and the main concern is identification and safe management of a male baby at risk of haemophilia. Women who have low levels of a clotting factor may have mild or severe bleeding phenotypes which may or may not improve in pregnancy; some clotting factors, such as factor XI, do not rise during pregnancy, while others, such as fibrinogen, increase significantly. In addition, there is less clear-cut available evidence-based guidance for the rare deficiencies.

3. Identification and assessment of evidence

This guideline was developed using standard methodology for developing Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects [DARE] and the Cochrane Central Register of Controlled

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Trials [CENTRAL]), EMBASE, MEDLINE and Trip were searched for relevant papers. The search was inclusive of all relevant articles published until March 2016. The databases were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings and synonyms, and this was combined with a keyword search. The search included the following terms: (haemophilia* or hemophilia* or bleeding disorder or bleeding disorders) AND (pregnan* or delivery or labor or labour or postpartum haemorrhage or postpartum hemorrhage). The search was limited to humans and papers in the English language. Relevant guidelines were also searched for using the same criteria in the National Guideline Clearinghouse and the National Institute for Health and Care Excellence (NICE) Evidence Search.

Where possible, recommendations are based on available evidence. Areas lacking evidence are highlighted and annotated as 'good practice points'. Different wordings are used (such as must, should, could, suggest, require); these are intentional to encourage an individualised approach where appropriate. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix I.

4. Haemophilia

4.1 What is the definition?

Clinicians should be aware that haemophilia is an X-linked condition associated with reduction or absence of clotting factor VIII (haemophilia A) or IX (haemophilia B), causing bleeding symptoms. ✓

Haemophilia is an X-linked bleeding disorder caused by a genetic mutation in either factor VIII (haemophilia A) or factor IX (haemophilia B) which causes absent or reduced production of that coagulation factor.[1–3] The hallmark of the condition is bleeding into joints and muscles.

4.2 How should inheritance be assessed?

Up to 50% of neonatal males with severe haemophilia have no previous family history. In these cases, there is a 90% chance that the mother is a carrier, with risk to the next male child. D

A family tree should be constructed to assess the likelihood of haemophilia carriership in at-risk female family members. ✓

Females at risk of carrying haemophilia, particularly severe haemophilia, should be tested for the genetic mutation present in affected family members, if available. ✓

Haemophilia A and haemophilia B are X-linked recessive conditions. A woman is an 'obligate carrier' for haemophilia A or B if her father has haemophilia or if she has an affected son and an affected relative(s) in the maternal line. A woman is likely to be a carrier if she has a single son with haemophilia or a single carrier daughter, but this is not always the case, as haemophilia may be the result of a new mutation in her offspring. A woman is a possible carrier if she has a maternal relative with haemophilia. For haemophilia A, a factor VIII:von Willebrand factor (VWF) ratio of less than 0.7 is suggestive of carriership but a ratio of more than 0.7 does not exclude it. Where possible, at-risk females should be tested for the genetic mutation responsible for the haemophilia in affected family members.

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Each son of a carrier female has a 50% chance of inheriting haemophilia from his mother; similarly, each daughter has a 50% chance of being a haemophilia carrier.[3]

Up to 50% of haemophilia cases have no previous family history, either owing to lack of male relatives or spontaneous mutation, which occurs in 40–50% of cases of severe haemophilia. Spontaneous mutations occur more commonly during spermatogenesis than oogenesis because of the high cell turnover and unpaired X chromosome. Therefore, new cases of severe haemophilia usually arise from mutation during spermatogenesis in the maternal grandfather, conferring obligate carrier status on the mother. This theory is correct in 90% of cases and thus, the risk to the next male baby after a spontaneously affected sibling is 45%.[4]

Evidence level 3

4.3 *What are the different phenotypes and how is severity assessed?*

Clinicians should be aware of the different phenotypes and severities of haemophilia, as this influences risk and required management. ✓

Severity is categorised according to the plasma concentration of factor VIII or IX. Severe haemophilia is defined as a factor concentration of less than 0.01 iu/ml; moderate haemophilia, 0.01–0.05 iu/ml; and mild haemophilia, 0.06–0.40 iu/ml. The bleeding phenotype can largely be predicted from the absolute concentration of factor. This is important when considering the risk of intracranial haemorrhage (ICH) and other bleeding at the time of delivery of an affected male (Appendix II). Males with severe haemophilia experience spontaneous bleeding into muscles and joints, and require regular prophylaxis with clotting factor replacement to help avoid arthropathy and neurovascular compromise.[5] Those with moderate and mild haemophilia may only bleed following trauma or invasive procedures, and require cover for these times. The causative mutation in the family influences severity of haemophilia and may also influence the bleeding phenotype in carriers.[6] The most significant complication of haemophilia is the development of antibodies (inhibitors) to the clotting factor preparations used for treatment. This occurs in around 10–40% of treated patients and involves both genetic and nongenetic factors.[7] Inhibitors may cause significant morbidity, require intensive management and are potentially life threatening. Inhibitor development in female carriers is extremely rare.

Evidence level 3

4.4 *What are the risks in pregnancy to mother and baby?*

Known or potential female carriers may have low factor VIII/IX levels. The levels should be checked prior to an invasive procedure or in association with bleeding symptoms. D

Clinicians should be aware that carriers of haemophilia are at increased risk of bleeding with invasive procedures, termination, spontaneous miscarriage and at the time of delivery. D

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Male neonates with haemophilia are at increased risk of bleeding, including ICH and extracranial haemorrhage (ECH). C

Male neonates with haemophilia are at risk of iatrogenic bleeding following delivery. ✓

Factor levels in female carriers are variable and unpredictable. Due to X-chromosome inactivation (lyonisation) which occurs in early embryonic life, levels are approximately half that of noncarriers, i.e. 0.5 iu/ml, although studies have shown that the median is in fact slightly higher at 0.6 iu/ml.[6,8] Families in which many females are low level carriers are thought to have co-inherited the haemophilia gene and a genetically controlled susceptibility to skewed lyonisation.[9] Other factors, such as ABO blood group, may also influence factor levels.[10] Levels largely correlate with bleeding risk and should be measured as early as possible in suspected carriers to inform risk during surgery or delivery. Bleeding risk can be increased in carriers even if they have relatively normal factor levels of 0.4–0.6 iu/ml (Appendix II).[6,8] Evidence level 3

Carriers of haemophilia A have an increased tendency to bleed with invasive procedures, even when their levels are between 0.4 and 0.6 iu/ml.[8] The risk of spontaneous miscarriage is not increased in haemophilia carriers, but if it occurs, bleeding is more likely to be heavy.[11] Although coagulation factors may normalise during pregnancy, they do not usually reach the levels seen in the general pregnant population and it may be for this reason, or an early fall in levels postnatally, that carriers of haemophilia have an increased risk of postpartum haemorrhage (PPH).[11]

Neonates are at risk of ICH and ECH as a consequence of the process of labour and delivery. In the general population, the risk of ICH is considered to be 0.058%[12–14] and of ECH, 0.469%.[15,16] The risk in babies affected with haemophilia is increased to 2.5% and 3.7%, respectively.[17–25] Thus, neonates with haemophilia have an odds ratio of 44 (95% CI 34.7–57.1) for ICH and 8 (95% CI 5.38–12.60) for ECH compared with the general population.[26] Evidence level 2+

Bleeding events in neonates with haemophilia differ from those in older children where muscle and joint bleeds predominate. In addition to the risks of cranial bleeding at delivery, neonatal bleeds are typically iatrogenic, arising as a consequence of venepunctures, intramuscular vitamin K and surgical interventions.[27,28] Evidence level 3

4.5 What is the prepregnancy management?

The baseline factor level should be determined prior to onset of pregnancy. ✓

Before pregnancy, the general health of women who are carriers for haemophilia should be optimised, including attention to weight and correction of any iron deficiency. ✓

Factor VIII levels increase with age, as well as inflammatory conditions, and an up-to-date level is required to assess risks in pregnancy. It is prudent to also check factor IX baseline rather than accepting a historical result.

The health of women who are carriers of haemophilia should be optimised before pregnancy, including addressing any iron deficiency and obesity, both of which are associated with an increased bleeding risk.[29] Evidence level 3

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4.6 *How should genetic counselling be provided?*

Genetic counselling should be provided to women at risk, ideally before pregnancy, by appropriately qualified and experienced clinical staff. ✓

Written informed consent should be obtained in advance of any genetic testing. ✓

The provision of appropriate counselling may require input from a multidisciplinary team of health professionals, for example, haemophilia clinical specialists, obstetricians and genetic counsellors.

Patients should be in a position to be able to make their own informed decision having been provided with all the appropriate information, and having been given the time and opportunity to have their questions answered. Information should be provided about inheritance, clinical aspects of haemophilia (such as bleeding, treatment and complications) and options available to family members who may wish to consider genetic diagnosis, including PND, and discussion about having a child with haemophilia. Ideally, counselling of haemophilia carriers should be carried out before pregnancy.

It is the responsibility of the referring clinician to ensure that appropriate informed consent is obtained for genetic diagnosis, including carrier and/or PND.

4.7 *What are the options for prenatal diagnosis (PND)?*

Carriers of severe haemophilia should be offered preimplantation genetic diagnosis. ✓

Carriers of severe haemophilia with a male fetus confirmed to be affected by haemophilia should be counselled to enable informed choices. D

All carriers of severe haemophilia should be offered fetal sex determination by free fetal DNA analysis from 9 weeks of gestation. D

Pregnant carriers of severe haemophilia with a male fetus at risk of haemophilia should be offered the option of PND with chorionic villus sampling (CVS) at 11–14 weeks of gestation. ✓

All carriers of haemophilia with male fetuses should be offered third trimester amniocentesis if diagnostic investigations have not previously been performed to determine haemophilia status to inform options for delivery. ✓

Options for PND in inherited bleeding disorders are summarised in Appendix III. These include noninvasive PND for fetal sexing, genetic analysis for the familial mutation in fetuses at risk of being affected by means of CVS or amniocentesis, and preimplantation genetic diagnosis.

In England, NHS England[30] will commission three cycles of preimplantation genetic diagnosis for couples at risk of and wishing to avoid the birth of an affected child. Success rates of around 30% have been reported.[31]

Carriers of male fetuses confirmed to be affected by severe haemophilia should be counselled to enable informed choices.[32]

Evidence level 4

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4.8 *What is the antepartum management?*

Antenatal care should be delivered in the context of a multidisciplinary team setting with haematologists and obstetricians with expertise in this field. ✓

Maternal factor VIII/IX should be checked at booking, before any antenatal procedure and in the third trimester; factor VIII levels rise in pregnancy, but factor IX tends to remain stable. D

Aim for factor VIII/IX levels of at least 0.5 iu/ml to cover surgical or invasive procedures, or spontaneous miscarriage. If treatment is required, factor levels of 1.0 iu/ml should be aimed for and not allowed to fall below 0.5 iu/ml until haemostasis is secure. C

Tranexamic acid should be considered in combination with treatment for all those with levels of less than 0.5 iu/ml or as sole therapy for those with levels above 0.5 iu/ml if clinically indicated. Following miscarriage, it should be continued until the bleeding settles. D

Desmopressin (DDAVP) can be used antenatally to raise factor VIII levels. Due to the antidiuretic effect, fluids should be restricted to 1 litre for 24 hours after use or, if not possible, electrolytes should be monitored. C

Recombinant factor VIII should be used if levels obtained with DDAVP are insufficient or in a known nonresponder. C

Recombinant factor IX is required to cover invasive or surgical procedures in women with factor levels less than 0.5 iu/ml. ✓

When giving treatment to raise clotting factor levels, it is important to monitor the response to treatment by measuring the plasma clotting factor concentration before and after infusion, and 4–6 hours following treatment to facilitate dosing. ✓

Following any invasive or surgical procedure, a plan for ongoing treatment is required to maintain the coagulation factor in the normal range for a suitable duration, determined by the nature of the procedure. ✓

A clear plan for the intrapartum care of a carrier and the baby should be available in advance of 37 weeks of gestation. The woman should be seen in the anaesthetic clinic and the neonatologists should be informed of the intended delivery of a baby with haemophilia. ✓

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If antenatal diagnosis has not been performed in a male fetus, then he should be managed as if he is affected. ✓

External cephalic version should be avoided in affected or potentially affected male fetuses and female fetuses who are obligate or possible carriers of severe haemophilia B. ✓

Close liaison within the multidisciplinary team is required in order to ensure the safety of both mother and baby at the time of delivery. Due to the risk of ICH in affected males at the time of delivery, the neonatal team should be informed of the expected date of delivery of a male with haemophilia and plans made for neonatal care, including the availability of an appropriate factor concentrate.[27]

Evidence level 3

Synthesis of factor VIII is increased in pregnancy with plasma levels rising from 6 weeks of gestation to two to three times the baseline by term. Factor IX levels are relatively unaltered.[11] For carriers of haemophilia A, the pregnancy-induced rise in factor VIII level reduces the risk of bleeding although they remain vulnerable in early pregnancy and those with low baseline levels (for instance, less than 0.15 iu/ml) may not achieve normal levels by delivery. Women with low factor IX levels remain at risk of bleeding throughout pregnancy.

Evidence level 2+

The normal range for factor VIII and IX outside of pregnancy is 0.5–2.0 iu/ml. A level above 0.5 iu/ml is likely to be sufficient for haemostasis during invasive procedures, such as amniocentesis and CVS. Since carriers may bleed with invasive procedures with levels around 0.5 iu/ml, this should be the absolute minimum tolerated for major procedures, such as lower segment caesarean section.[6] If treatment is required, factor levels of 1.0 iu/ml should be aimed for and not allowed to fall below 0.5 iu/ml.

Tranexamic acid is an antifibrinolytic agent which is associated with reduced bleeding in menorrhagia, surgery and trauma.[33] It is useful as sole therapy for women with low normal factor levels or may be used in combination with other treatments in women at higher risk.

Evidence level 4

DDAVP is a synthetic analogue of vasopressin which can increase the levels of both factor VIII and VWF three- to four-fold.[34] It has no effect on factor IX. The mechanism of action of DDAVP is poorly understood,[35,36] although it exerts its action through V2 receptors on endothelial cells. The uterus expresses V1 receptors, for which DDAVP has no affinity and, therefore, its use in pregnancy is considered safe.[37–39] DDAVP can be used to raise factor VIII levels for invasive procedures during pregnancy and at the time of delivery.[40] DDAVP should be used at a dose of 0.3 micrograms/kg of prepregnancy weight as an intravenous or subcutaneous injection. Repeated doses may be given 12–24 hourly, but may lead to tachyphylaxis (where the factor VIII response lessens with further doses). It is essential to monitor the response with factor VIII assays before and after treatment to ensure adequate levels.[35,41] DDAVP has antidiuretic properties which may result in hyponatraemia. Hyponatraemic fits have occurred following administration of DDAVP.[36,37] Therefore, fluids should be restricted to 1 litre for 24 hours following treatment and DDAVP should be avoided in women with pre-eclampsia. During intravenous infusion, hypotension, headache and facial flushing are common, but generally mild. Blood pressure should be monitored before and after infusion. Women with factor VIII levels less than 0.5 iu/ml in the third trimester should be considered for DDAVP in the first instance. However, if contraindicated or if levels obtained with DDAVP are insufficient, as a result of tachyphylaxis or in a known nonresponder, then recombinant factor VIII should be used.

Evidence level 2+

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As endogenous factor IX does not increase, carriers of haemophilia B with factor IX levels less than 0.5 iu/ml require treatment with recombinant factor IX to maintain levels above 0.5 iu/ml for invasive procedures.

Response to treatment (recovery) and duration (half-life) varies among individuals and within individuals in different circumstances. The clinical setting can influence the clotting factor half-life, for example, this can be shorter in the immediate period following surgery or delivery.

In general, following a surgical procedure, treatment is directed at maintaining levels of coagulation factor above 0.5 iu/ml for 3–5 days to allow for wound healing, but this should be individualised according to the clinical situation.

Consideration of mode of delivery should take into account risks of maternal and fetal morbidity, and should be discussed with the mother by the multidisciplinary team in advance. A written plan for delivery should be available in the maternal record. The plan should detail the requirements with regard to central neuraxial anaesthesia and for clotting factor replacement at the time of delivery. She should be reviewed by an anaesthetist. For the baby, it should state the precautions required for vaginal delivery and if there is need for assessment of clotting factor level from a cord sample at the time of delivery, as well as any other recommendations regarding early neonatal management.[42]

Evidence level 4

There is no evidence for the use of external cephalic version in pregnancies where the fetus has a bleeding disorder. In a meta-analysis of 84 studies that included 12 955 women, the overall complication rate was 6% and the rate of serious complications was 0.24% (placenta abruption in 0.18% and stillbirth in 0.6%). Ten of the 11 abruptions resulted in emergency caesarean section.[43,44] Although intracranial bleeding is not reported as a significant complication in these studies, external cephalic version has always been avoided in the case of a known/suspected fetus with a bleeding disorder due to this theoretical risk.

4.9 What is the optimal mode and timing of delivery?

A decision regarding the timing and mode of delivery should be agreed jointly between the woman and the multidisciplinary team. C

The option of a planned lower segment caesarean section should be discussed for the delivery of affected male babies, especially those with severe haemophilia and/or if the fetal status is unknown. However, there needs to be a full assessment of the advantages and disadvantages of this mode of delivery and consideration of obstetric factors, maternal bleeding risk, patient preference and reproductive expectations. D

If elective caesarean section is intended, this should be at 39^{+0} completed weeks with a clear plan for the event of spontaneous labour occurring beforehand. D

For intended vaginal delivery, spontaneous labour is preferred, if no other obstetric concerns, to minimise the risk of intervention. Measures should be taken to ensure expertise and necessary resources are available at all times. Planned induction of labour may be necessary in cases where there are concerns about distance of travel to the specialist centre or if there are other obstetric concerns. D

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The use of ventouse and midcavity forceps should be avoided for male babies at risk of haemophilia. B

Fetal blood sampling (FBS) and fetal scalp electrode (FSE) should be avoided in babies expected to have severe or moderate haemophilia. In babies potentially affected with mild haemophilia, judicious use of FBS and FSE can be considered, in order to facilitate vaginal delivery and avoid morbidity associated with caesarean section in labour. This decision should be made by a senior obstetrician. Where FBS is used, sustained pressure under direct vision should be used to ensure haemostasis. ✓

The plan for intrapartum management and the second stage of labour, involving a senior obstetrician, should be documented. ✓

There is no evidence to recommend special measures for delivery in women carrying female fetuses. A female fetus who is at risk of carrying severe haemophilia B may theoretically be more at risk of ICH/ECH and this should be considered in the birth plan. ✓

The optimal mode of delivery for a carrier may be affected by obstetric considerations, the woman's own personal wishes and logistical factors, such as where the family reside in relation to the most appropriate delivery unit. Therefore, the mode of delivery should be discussed with the woman and multidisciplinary team, taking into account individual factors, including bleeding risk to the baby according to the stratification tables (Appendix II and IV) and obstetric issues, such as fetal presentation, prior labour experience and maternal risk, as well as future reproductive expectations.[45]

A number of publications have reported the relationship between mode of delivery and the risk of ICH and ECH in neonates in the general population and in those with inherited bleeding disorders. In a large retrospective population study of liveborn singleton infants, the risk of ICH was highest in babies delivered by forceps, ventouse extraction and emergency caesarean section during labour. Elective caesarean section was associated with the lowest risk, followed by uncomplicated vaginal delivery. This translated to odds ratios, compared with uncomplicated vaginal delivery, of 2.86 (95% CI 1.87–4.37) for forceps delivery, 2.21 (95% CI 1.68–2.91) for vacuum extraction and 2.10 (95% CI 1.64–2.68) for caesarean section during labour. Sequential instrumentation (vacuum and forceps) had the highest odds ratio of 7.45 (95% CI 4.06–13.68), whereas the odds ratio for a planned caesarean section was 0.69 (95% CI 0.39–1.24).[14] Evidence level 2++

The increased risk of bleeding in association with assisted vaginal delivery has been demonstrated in a cohort of babies with haemophilia; among six babies who developed intra- or extracranial bleeding, four were born by assisted vaginal delivery, one by emergency caesarean and one by uncomplicated vaginal delivery. All cases had no known family history of haemophilia.[45] A United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) survey of the neonatal outcomes of babies born with severe haemophilia in UK haemophilia centres between 2003 and 2013 has shown an incidence of ICH in haemophilia A of 6.2/1000 patient years (95% CI 4.32–8.95) and for haemophilia B, 4.1/1000 patient years (95% CI 1.5–10.81). Of 17 recorded cases of ICH, nine occurred in association with spontaneous vaginal delivery (SVD), four with assisted vaginal delivery (these males had no known family history of haemophilia), three with elective caesarean section and one with emergency caesarean section. Interestingly, two of these cases had no prior family history of haemophilia and for the third, it is not known.

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Retrospective studies of babies with haemophilia have confirmed the highest risk from assisted vaginal delivery, especially ventouse. However, it has been more difficult to define the relative risk of ICH in uncomplicated SVD compared with caesarean section, and there is a lack of data comparing emergency and elective caesarean delivery. There is, therefore, considerable debate about the best mode of delivery for babies affected with haemophilia.[46–48] In the literature, two cases of ICH have been reported in 283 neonates with haemophilia delivered by caesarean section; one was a preterm baby delivered at 27 weeks of gestation, while 22 cases of ICH have been reported among 816 affected babies delivered by SVD.[23–25,49] A systematic review of the literature and meta-analysis showed the lowest risk of ICH with caesarean section, with an odds ratio of 0.34 (95% CI 0.14–0.83).[26] A multicentre study in the Gulf region, where over 80% of women deliver vaginally due to the cultural desire for large families, showed ICH in 5/163 (3.1%) neonates with severe haemophilia; 2/131 (1.5%) from uncomplicated vaginal delivery; 2/6 (33.3%) from instrumental delivery; and 1/26 (3.8%) from caesarean section although this was a preterm baby of 32 weeks of gestation.[50]

Evidence level 3

Ventouse and midcavity or rotational forceps are associated with a significantly increased risk of ICH and should be avoided.[14,49,51,52] Low-cavity forceps may be used and are likely to be preferable to caesarean section in the second stage of labour.

Evidence level 2+

A planned caesarean section should be offered for the delivery of affected male babies, especially those with severe and moderate haemophilia. However, there needs to be a full discussion of the advantages and disadvantages; caesarean section is associated with an increase in fetal and maternal morbidity,[53] which escalates with multiple repeat caesarean deliveries.[54] The optimal mode of delivery will depend on maternal and fetal bleeding risks (Appendix II and IV), prior labour experience and reproductive expectations.

Caesarean section prior to 39^{+0} completed weeks of gestation increases the risk of neonatal respiratory morbidity.[55–57] ICH is also increased in prematurity.

Evidence level 4

Induction of labour is not routinely indicated, however, timed delivery in order to optimise the available expertise, may be preferable to ensure robust out of hours arrangements.[58,59]

Evidence level 2+

There is a lack of good quality data reporting the risk of haemorrhage with the use of FBS or FSE in babies at risk of bleeding disorders. Two case reports were identified where FBS was associated with scalp haemorrhage in babies postnatally diagnosed with haemophilia.[60,61] One case series reported the use of FBS in an affected male baby with no adverse consequences.[52] There were no identified case reports of bleeding secondary to the use of FSE in fetal bleeding disorders.

Evidence level 4

The cut-off value for predicted factor VIII or IX level, above which no birth restrictions are necessary, has not been defined. Although mild haemophilia is unlikely to be associated with severe bleeding at birth (Appendix II).

Prolonged labour is associated with an increased risk of uterine atony and the need for instrumental vaginal delivery, thereby increasing bleeding risk to both mother and baby.[62] Since the use of ventouse extraction, midcavity forceps and, in many cases, invasive fetal monitoring are contraindicated when the fetus is known or suspected to have haemophilia, the chance of emergency caesarean section is increased.

Evidence level 4

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Female fetuses who are carriers have a small risk of very low factor levels due to extreme lyonisation, but this needs to be weighed up against the possibly greater risks of withholding instrumental delivery and invasive fetal monitoring. As factor IX levels are lower at birth and are not increased by the stress of delivery, female carriers of severe haemophilia B are theoretically at higher risk. A consultant obstetrician should be involved for decision making during labour.[63]

Evidence level 4

4.10 How can analgesia and anaesthesia be managed safely?

Factor VIII/IX levels of more than 0.5 iu/ml are required for the insertion and removal of epidural catheter and for spinal anaesthesia.

D

Experienced clinicians should be involved in decisions about whether or not to perform a central neuraxial anaesthetic technique, and the woman should be given all the information she needs to make an informed choice.

✓

The most suitable form of analgesia depends on the context of the delivery. All carriers should have the opportunity to discuss analgesia with a senior anaesthetist prior to delivery. A clear plan for analgesia and anaesthesia should be available in the maternal records.

D

Intramuscular injections should generally be avoided if factor VIII/IX levels are less than 0.5 iu/ml. They may be used when a woman's factor VIII/IX is maintained in the normal range by clotting factor support or DDAVP.

✓

One of the complications of central neuraxial blockade is the development of compressive epidural haematoma with subsequent neurological injury. The third National Audit Project identified the incidence of vertebral canal haematoma after central neuraxial blockade in all patients as 0.85/100 000 (95% CI 0.0–1.8 per 100 000).[64] Ruppen et al.[65] reviewed the incidence of epidural haematoma, infection and neurological injury after central neuraxial blockade for obstetric indications in 27 studies of 1.37 million women and found an incidence of epidural haematoma of 1 in 168 000.

Evidence level 3

There are inherent problems in making recommendations about the safety of performing central neuraxial blockade in patients with abnormalities of coagulation. The rarity of the abnormality in combination with the infrequent nature of the complication means that it is difficult to make accurate estimates of the incidence of complications related to the abnormality of coagulation. Factor levels of more than 0.5 iu/ml are considered adequate for all types of neuraxial anaesthesia although the evidence for this is limited, being restricted to case reports and small case series.[66] This would also apply to the removal of the catheter where bleeding risk is similar, if not slightly greater. 'Single shot' spinal and epidural anaesthesia avoid this concern, but require repeated procedures if prolonged anaesthesia is needed.

Evidence level 4

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These considerations have been extensively discussed in the national guideline on 'Regional anaesthesia and patients with abnormalities of coagulation'.[67] They state that there may be circumstances in which although the use of a regional technique for a patient with abnormal coagulation may put the patient at significant risk as a result, the alternative for this patient (often a general anaesthetic) may expose them to even greater risk. While the guideline focuses on acquired disorders of haemostasis, the principles outlined in the document can be extended to the delivery of central neuraxial blockade in pregnant women with inherited bleeding disorders.

Knowledge of the factor VIII/IX level at 32–34 weeks of gestation allows the anaesthetist to discuss the possibilities for analgesia and anaesthesia. Epidural analgesia is the most effective form of pain relief in labour. In addition, there is clear evidence of the safety of central neuraxial blockade (epidural and spinal anaesthesia) compared with general anaesthesia for caesarean section.[64] National recommendations are that more than 95% of category 4 (planned) caesarean sections and more than 85% of category 1 caesarean sections (performed where there is an immediate threat to the life of the mother or the baby) be performed under central neuraxial blockade.[67]

Evidence level 4

Intramuscular injections may be associated with painful haematomas although a study in haemophiliac boys suggested that the risk was overestimated.[68] In general, they should be avoided when the clotting factor levels have failed to normalise and have not been maintained in the normal range by clotting factor support or DDAVP. However, they may be considered after risk/benefit analysis if not giving the intramuscular medication poses additional risks.

4.11 What is the haemostatic management during labour?

If clotting factor levels are less than 0.5 iu/ml, DDAVP should be given to raise factor VIII, or factor IX concentrate should be given to raise factor IX, aiming for 1.0 iu/ml. ✓

Tranexamic acid could be considered as sole therapy for women with low normal levels or in conjunction with DDAVP to increase factor VIII, or with substantive factor IX treatment. ✓

Treatment should be given as close to delivery as possible. ✓

DDAVP should be used to raise factor VIII levels. Factor IX does not respond to DDAVP and factor concentrate is required to raise factor IX levels (see section 4.8). The authors consider the optimal timing for treatment to be after the point of established labour.

There is limited evidence for the use of tranexamic acid in PPH, but systematic reviews suggest probable efficacy in the absence of clear safety concerns (see section 4.12).[69–71] If tranexamic acid is administered at the onset of established labour by intravenous injection, then it is able to exert an antifibrinolytic effect immediately, at the time of placental separation.

Evidence level 2+

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4.12 *What is the postpartum management?*

To minimise the risk of PPH, it is important to recommend/offer active management of the third stage of labour. ✓

Levels of factor VIII/IX should be maintained above 0.5 iu/ml for at least 3 days following an uncomplicated vaginal delivery or 5 days following instrumental delivery or caesarean section. Management should be guided by results of factor assays. D

Tranexamic acid should be continued postpartum until lochia is minimal. B

Pharmacological thromboprophylaxis should generally be avoided where the factor level is 0.6 iu/ml or less, but will need to be considered in women with thrombotic risk factors, with careful balance of risks. ✓

Following discharge from hospital, the haemophilia centre should maintain contact with the woman who should be advised to report any increase in postpartum blood loss. ✓

The risk of bleeding in carriers of haemophilia is increased for both primary and secondary PPH.[52] Those with low levels in the third trimester can have higher risk even following factor concentrate.[72] Carriers should be identified as being at increased risk of PPH and offered uterotonics for the third stage of labour.[73]

Clotting factor levels fall from 2 days postpartum and although the mechanism for cessation of bleeding is largely mechanical (through uterine contraction), borderline levels of factor VIII and IX are associated with increased risk of PPH.[6] Thus, haemostatic levels should be maintained in the initial postpartum period. Where treatment has been given, a factor assay should be repeated 6–12 hours later and top-up treatment given if needed, as consumption of factor can be greater during this time. For caesarean section and other surgical procedures, levels should not be allowed to fall below 0.5 iu/ml for at least 5 days, to ensure adequate haemostasis.[74]

Evidence level 4

There is limited evidence for the use of tranexamic acid in PPH, but systematic reviews suggest probable efficacy in the absence of clear safety concerns.[69–71] There appears to be no long-term adverse outcome for children whose mothers took tranexamic acid while breastfeeding.[63] Women should be advised to take tranexamic acid following delivery until the bleeding has become like their usual menstrual period or until the bleeding has stopped. Following caesarean section, tranexamic acid should be taken for a minimum of 7 days postoperatively (see section 5.5).

Evidence level 2+

If factor VIII or IX levels have normalised, or treatment given to ensure a minimum level of 0.5 iu/ml, then it is possible that the risk of venous thromboembolism may outweigh the risk of PPH. However, the risk of secondary PPH may be high even despite replacement therapy[72] and therefore, a careful assessment of blood loss and thrombotic risk should be performed daily, and thromboprophylaxis prescribed if indicated.

Carriers of haemophilia have an increased duration of lochia, ranging from 21–58 days.[75] A woman should be advised that the rate of blood loss should lessen over time. If the rate of blood loss increases or changes to become bright red, the woman should present for assessment of clotting factor level and of any obstetric cause of an increase in bleeding.[73]

Evidence level 4

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4.13 *What is the neonatal management?*

A plan for diagnostic testing of the neonate following delivery, including cord blood sampling, should be included in the maternal pregnancy management plan. ✓

Coagulation results in neonates should be interpreted against age-adjusted reference ranges. D

Cord blood sampling and diagnostic testing is recommended for all male babies born to mothers who are carriers of haemophilia A/B although some mild cases may require retesting at 3–6 months of age. D

Cord blood sampling and diagnostic testing of female babies born to mothers who are carriers of haemophilia is not recommended. D

Parents of neonates diagnosed with haemophilia should be informed of the diagnosis in a timely manner and arrangements should be made for neonatal follow-up at a haemophilia centre. ✓

In a neonate with low factor levels, vitamin K should be administered by an oral regimen and following neonate bloodspot screening, pressure should be sustained to avoid excess bleeding. ✓

Cranial ultrasound (US) should be considered prior to discharge in all neonates with severe or moderate haemophilia. ✓

Cranial magnetic resonance imaging (MRI) should be undertaken in neonates with symptoms or signs suggestive of ICH even in the presence of a normal cranial US. D

In neonates with haemophilia, information on the symptoms and signs of ICH should be provided at the time of discharge. ✓

Short-term primary prophylaxis should be considered in severe and moderate haemophilia in infants considered to be at increased risk of bleeding due to trauma at delivery or prematurity. D

Clinical bleeding events in neonates with haemophilia should be managed in accordance with treatment guidelines. D

Neonate males with haemophilia, especially those with severe and moderate disease, are at increased risk of haemorrhage in the neonate period. It is therefore important that, if haemophilia is suspected, the diagnosis is confirmed soon after birth, as this will facilitate appropriate management (Appendix V). However, it should be noted that 50% of haemophilia cases arise without a family history and are not anticipated antenatally.[4]

Evidence level 3

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Haemostatic proteins are significantly affected by gestational and postnatal age. The diagnosis of haemophilia during the neonatal period requires an understanding of the effect of age on the haemostatic system and the use of appropriate age-adjusted normal ranges.[76]

It may not always be necessary or informative to test for mild haemophilia during the neonatal period. This will depend on the severity in the family and the likelihood of being able to make a diagnosis in this age group (see Appendix V).

Evidence level 2–

Where testing is appropriate at birth, it is usually suggested that a cord blood sample is obtained following delivery to avoid the potential trauma of venepuncture. However, an abnormal result should be verified by a venepuncture sample. Molecular diagnostic studies can also be useful in some cases.[27]

In normal neonates, factor VIII levels are within the normal adult range at birth, whereas factor IX levels are usually about 50% of adult values and are further reduced in preterm neonates. It is therefore possible to confirm a diagnosis of severe or moderate haemophilia A in a neonate regardless of the gestational age. In mild haemophilia A, due to the stress of delivery, factor VIII levels may be normal and repeat testing is recommended at 3–6 months of age.[27]

It is usually possible to diagnose severe and moderate haemophilia B at birth, but confirmation of mild haemophilia B is complicated by overlap with normal values, necessitating repeat testing at 3–6 months of age or molecular analysis if the genetic defect is known.[27]

The risk of bleeding in female neonates who are obligate or potential carriers of haemophilia A or B appears to be very low and neonate screening is therefore not routinely advised.[27]

Evidence level 4

Intramuscular vitamin K can result in localised bleeding in babies with haemophilia, including muscle haematomas.[77] Intramuscular vitamin K should therefore be withheld until the results of diagnostic investigations are available, but if there is likely to be a significant delay, oral vitamin K should be administered. If haemophilia is diagnosed, oral vitamin K should be administered according to a standard regimen. Administration of 1 mg oral vitamin K is as efficient as intramuscular administration of the same dose in the prevention of classical haemorrhagic disease in the neonate.[78]

Evidence level 3

Given the risk of ICH in neonates with severe inherited bleeding disorders, cranial US has been proposed as a possible screening test for early detection of ICH. Although readily available and easy to perform, there are inadequate data to allow the efficacy of this type of screening to be assessed and there is no consensus on the optimal timing of screening. It should also be noted that cranial US is not the most sensitive imaging technique for the detection of subdural haemorrhage, which is the most common site of bleeding. Despite these reservations, cranial US may be considered prior to discharge in neonates with severe and moderately severe disorders.

Alternative scanning techniques, including MRI, have been used in normal neonates and demonstrate that bleeding is not uncommon following delivery, is usually clinically silent and resolves on follow-up imaging. There are no published data on neonates with inherited bleeding disorders. At the present time, routine MRI scan is not advised, but should be considered in any infant with symptoms or signs suggestive of ICH.[27]

Evidence level 4

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It is not currently standard practice to administer short-term prophylaxis with factor concentrate in severe or moderate haemophilia, and there are no data with which to assess effectiveness and no agreed regimen. Prophylaxis should, however, be considered where there has been trauma at delivery (for example, following instrumental delivery or prolonged second stage of labour) and in preterm infants.[27]

Evidence level 3

5. von Willebrand disease (VWD)

5.1 What is the classification and inheritance?

VWD is classified according to whether the deficiency of VWF is partial quantitative (type 1), qualitative (type 2) or severe quantitative (type 3). The classification is important for diagnosis, treatment and counselling of patients. However, it does not reliably predict response to therapy and has a variable association with VWF gene mutations.

B

Clinicians counselling these women should be aware that inheritance of VWD is autosomal and variably dominant or recessive, depending on the VWD type.

✓

Genetic counselling about the risk of disease transmission, and its variable penetrance and expression, should be provided for all women with VWD.

✓

VWD results from a quantitative or qualitative deficiency of VWF, which is a large and complex glycoprotein essential for platelet-dependant primary haemostasis and also for carriage of factor VIII in the circulation. VWD is considered to be the most common inherited bleeding disorder. The prevalence of clinically relevant VWD is no more than 1/10 000 but less symptomatic cases might be more prevalent, up to 1/1000.[79] It is classified according to the nature of the deficiency; the diagnostic approach to VWD has been reviewed by Ng et al.[80]

Clinically relevant type 1 VWD is a partial quantitative deficiency of VWF characterised by concordant reductions in VWF protein and functional activity levels of less than 0.3 iu/ml. The relationship between VWF level and VWD phenotype is only partially explained by specific VWF gene mutations as there are multifactorial genetic and environmental influences on VWF levels. Inheritance of type 1 VWD is therefore not straightforward, and is characterised by variable penetrance and expressivity of the VWD phenotype. It is now recommended that patients with a bleeding history and VWF activity of 0.3–0.5 iu/ml should be regarded as having 'low VWF' rather than VWD.[81] Alternative causes for bleeding, such as platelet function defects, should be sought in these borderline patients and a well taken bleeding history in the subject and family, using a standardised bleeding score, will help to assess risk. When VWF levels are less than 0.3 iu/ml, the likelihood of there being a mutation in the VWF gene is far greater and the pattern of inheritance in such cases is likely to be autosomal dominant and penetrant.[82–84]

Evidence level 1+

Type 2 VWD results from a variety of qualitative VWF defects, which usually demonstrate discordant reductions in VWF functional activity (VWF activity:VWF antigen ratio of less than 0.6). The principal abnormality may be a selective loss in high-molecular-weight VWF multimers, as seen in type 2A VWD, increased or reduced binding to platelet glycoprotein (GP) Ib (types 2B and 2M VWD, respectively), or reduced binding to factor VIII (type 2N VWD).[80]

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Inheritance of type 2 VWD is generally dominant. Genetic diagnosis is generally not clinically helpful. Thrombocytopenia may be exacerbated during pregnancy in patients with type 2B VWD and careful monitoring of VWF levels and platelet count is essential.[85]

Type 2N VWD has recessive inheritance. Recognition and differentiation of type 2N VWD from haemophilia A or from a haemophilia A carrier is required for valid genetic counselling, accurate carrier diagnosis and appropriate treatment of bleeding episodes. Genetic diagnosis has an important role to inform genetic counselling in type 2N VWD.[85,86]

Evidence level 4

Type 3 VWD is characterised by virtually absent VWF and consequently, significantly lowered factor VIII levels. The prevalence of type 3 VWD in the UK is around 1/1 000 000 of the general population although more frequent in communities where consanguineous marriages are common.[81]

Evidence level 1+

Type 3 VWD has recessive inheritance, with frequent consanguinity. Genetic diagnosis has important applications to inform genetic counselling, to identify asymptomatic carriers and to provide information regarding options for PND (first trimester via CVS or third trimester via amniocentesis to inform clinical management of childbirth—see Appendix III).[87]

Evidence level 4

5.2 What are the risks in pregnancy to mother and baby?

Clinicians should be aware that women with VWD have an increased risk of antepartum, primary and secondary PPH.

B

All women should receive counselling about risks of increased bleeding, especially women with type 1 VWD whose VWF level does not rise above 0.5 iu/ml by term, or type 2 or 3 VWD.

B

VWF and factor VIII levels start to rise from early first trimester and rise progressively throughout pregnancy to two to three times the baseline value at term.[88] This rise is usually adequate to rectify the VWF deficiency in many patients with type 1 VWD, in whom levels normalise by the time of delivery. However, in patients with severe VWF deficiency, for example, a baseline VWF level of less than 0.15 iu/ml, VWF and factor VIII levels may fail to normalise.[89] In patients with type 2 VWD who exhibit qualitative abnormalities of VWF, the abnormalities may not correct and may even worsen.[90] This is especially the case in type 2B VWD where thrombocytopenia, with its attendant increase in bleeding risk, may be aggravated by the rise in dysfunctional VWF.[85] In type 2N VWD, because the defect is due to impaired binding of the abnormal VWF, the factor VIII levels do not rise. In patients with type 3 VWD there is minimal or no rise in VWF levels.[91] Levels of VWF and factor VIII start to fall at around 3 days after delivery,[92] but the time to return to baseline varies between a few days and several weeks.[88,93–95]

Evidence level 2

During pregnancy and childbirth, women with VWD have a significantly increased risk of bleeding; antepartum haemorrhage is increased ten-fold, primary PPH occurs in 15–30% of women, while secondary PPH occurs in approximately 25%. The need for blood transfusion is increased five-fold and mortality rate is increased ten-fold compared with women without VWD.[96] Although perineal haematoma is a rare complication of normal vaginal delivery, a higher frequency of this has been observed in women with VWD. However, there does not appear to be an increased risk of miscarriage, preterm labour, placental abruption, fetal growth restriction or intrauterine fetal death.[97] Where miscarriage does occur, this can be complicated by significant bleeding.[91]

Evidence level 3

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Neonatal VWF levels are physiologically increased at birth. This confers some protection against bleeding, but it can make the diagnosis of VWD difficult during the neonatal period.[97] Neonates with type 2, type 3 and more severe type 1 VWD will have reduced levels at birth and may be at increased risk of bleeding. Despite this theoretical risk, bleeding problems in neonates with VWD, including type 3 disease, appear to be uncommon, and life-threatening bleeding secondary to ICH has only been reported very rarely and cases have often had additional risk factors for bleeding. In a single centre experience of six cases of VWD with ICH reported from Canada, no cases presented neonatally, and in a UK survey of ICH in children with inherited bleeding disorders, there were no neonatal cases with VWD.[98,99]

Evidence level 3

5.3 What is the prepregnancy and antenatal management?

Prior to conception, the bleeding phenotype should be assessed, historical diagnosis reviewed and response to DDAVP established. D

Safe management requires a multidisciplinary approach. ✓

All women with VWD should have VWF antigen levels and activity, and factor VIII levels checked at booking, in the third trimester and prior to any invasive procedures. ✓

Women with type 1 VWD who achieve normal VWF levels can be safely managed in standard obstetric units in collaboration with haemophilia centre staff. ✓

Women with types 2 and 3, or severe type 1 VWD should be referred for prenatal care and delivery to a centre where there are specialists in high-risk obstetrics, as well as a haemophilia centre. Facilities for laboratory monitoring of VWF and factor VIII levels are essential. D

Clinicians should aim for factor VIII and VWF ristocetin cofactor (VWF:RCo) activity levels of 0.5 iu/ml or above to cover surgical procedures or spontaneous miscarriage. ✓

Where invasive procedures are required, if VWF activity or factor VIII levels are less than 0.50 iu/ml, women should receive haemostatic support in the form of DDAVP, where responsive, or VWF-containing concentrates. ✓

Treatment should be with DDAVP in preference to blood-derived factor concentrates where possible. This is safe for use in pregnancy and at delivery, but should be avoided in pre-eclampsia. D

Fluid intake should be restricted to 1 litre for 24 hours following DDAVP administration to prevent maternal hyponatraemia. If additional fluid is required, electrolytes should be monitored. D

Clinicians should be aware that patients with type 2B VWD may develop thrombocytopenia following DDAVP treatment. D

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If VWF replacement therapy is required, a concentrate containing factor VIII and VWF, manufactured from a safe plasma source with adequate viral testing and inactivation procedures should be used. ✓

Target peak VWF activity levels should be 1.0 iu/ml and levels maintained above 0.5 iu/ml until haemostasis is secured. ✓

For most antenatal procedures, a single preoperative treatment is sufficient, but in some cases, a second dose may be required at 12–24 hours, depending on the nature of the procedure and the measured levels. ✓

In light of the reclassification of mild VWD that occurred in 2014,[80] the fact that levels increase with age[100] and variable bleeding phenotypes, any historical diagnosis should be reviewed prior to pregnancy. The severity of the bleeding phenotype should be reassessed, including personal bleeding history and response to previous haemostatic challenges. Bleeding scores, such as the bleeding assessment tool endorsed by the International Society on Thrombosis and Haemostasis, may be helpful in predicting the likelihood of a bleeding disorder.[101,102] Baseline investigations and accuracy of diagnosis should be checked.

Evidence level 4

Iron deficiency is common in patients with VWD due to heavy menstrual bleeding.[103,104] Haemoglobin level and iron status should be checked and iron supplements given if necessary.

Evidence level 3

Where plasma products have already been used in the past, screening for transfusion-transmitted infections should be performed. Vaccination to hepatitis A and B should be done if not already immune and consent for administration of plasma-derived concentrate should be obtained after the counselling of risks.

Safe management of VWD requires a multidisciplinary approach involving the haemophilia team, laboratory staff, obstetricians, midwives, anaesthetists and neonatologists. The patient should be fully informed of potential bleeding risks and the plan for management of pregnancy, delivery and the postpartum period. This should begin prior to conception and should be reviewed as pregnancy advances.

There is variability in haemostatic response to pregnancy in different types and subtypes of VWD. In normal women, VWF and factor VIII increase significantly with levels exceeding 1 iu/ml by term. In type 1 VWD, a progressive increase of VWF and factor VIII levels also occurs, with levels reaching greater than 0.5 iu/ml in most women.[90] However, caution should be exercised because there is heterogeneity of phenotypes and genotypes underlying type 1 VWD and careful evaluation of all pregnant women with a diagnosis of VWD is recommended. In general, women with levels at baseline of VWF and factor VIII of more than 0.3 iu/ml are likely to achieve normal levels at the end of pregnancy.[105] There is usually poor increment in women with a basal level less than 0.15–0.2 iu/ml.[89,106] In type 2A VWD and type 2M VWD during pregnancy, the defect does not correct. A significant increase of factor VIII and VWF antigen occurs, but VWF activity remains markedly reduced.

Most women with type 1 VWD achieve levels above 0.5 iu/ml by term and can be delivered as normal with central neuraxial anaesthesia if needed.[89]

Evidence level 3

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DDAVP

DDAVP is generally safe in pregnancy and at delivery[37,88,107] at a dose of 0.3 micrograms/kg of prepregnancy body weight, administered intravenously or subcutaneously. The advantages of DDAVP are its wide availability and most importantly, the avoidance of blood products.

Response to DDAVP can be variable in different types. DDAVP may not be suitable in patients with baseline VWF or factor VIII levels of less than 0.15 iu/ml as they may not achieve sufficient post-infusion levels for haemostasis. The best way to predict response to DDAVP is to carry out a trial infusion once type 2B has been excluded. In particular, as shown by Rodeghiero et al.,[108] the response is consistent over time in the same patient and the response pattern is reproducible within the patient's affected relatives.

DDAVP increases the VWF level by three- to five-fold, which normalises VWF and factor VIII levels in most cases of type 1 and some subcategories of type 2. Some subtypes of type 1 VWD, such as VWD Vicenza, show decreased survival of endogenously produced VWF following DDAVP as compared with normal survival of exogenously administered clotting factor concentrates. However, successful management of delivery with DDAVP has been described in VWD Vicenza despite the basal factor VIII/VWF not rising significantly in pregnancy.[109] In type 2B VWD, a transient thrombocytopenia occurs frequently after DDAVP administration and the therapeutic response is poor, therefore, it is not usually recommended for type 2B.[110] In type 2N VWD, the abnormal binding of factor VIII to VWF shortens the response. DDAVP should not be used in type 3 VWD patients as they lack releasable stores of VWF and do not respond to DDAVP.

Evidence level 3

Treatment with DDAVP should be avoided in patients who are intolerant or show adverse effects. It should also be avoided in women with pre-eclampsia.[107] There are anecdotal reports of myocardial infarction, and DDAVP should be avoided in patients known to have arterial disease or uncontrolled hypertension.[111,112] During intravenous infusion, hypotension, headache and facial flushing are common, but generally mild. Blood pressure should be monitored before and after infusion. Fluid intake should be restricted to 1 litre for the following 24 hours to prevent maternal hyponatraemia. Repeated administration should be carefully monitored as there is a potential for tachyphylaxis with declining response.[106,113]

VWF concentrates

There are many situations where DDAVP may be contraindicated or ineffective, and replacement with VWF concentrates is necessary in these cases. VWF concentrates usually contain factor VIII as well as VWF. Several different licensed plasma-derived high purity and intermediate purity VWF-containing concentrates are available. These concentrates are available as lyophilised powders and can be administered by slow bolus intravenous infusion after reconstitution with water for injection. The amount of factor VIII varies widely between different preparations and the VWF antigen/VWF:RCo ratio should be taken into consideration. For example, with high purity VWF concentrates, with little factor VIII, it may take more than 12 hours for the factor VIII to rise to normal.[114,115]

Evidence level 3

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VWF concentrates are pooled plasma products and all available concentrates have an excellent safety record. They undergo viral inactivation measures, which are integral to the manufacturing process; however, some viruses, such as parvovirus and hepatitis A, are relatively resistant to these inactivation techniques. No cases of HIV, hepatitis B or hepatitis C have been documented, despite decades of use.[115]

Evidence level 3

5.4 What is the intrapartum management?

The timing of treatment should be as near to delivery as possible, and pre- and post-treatment levels of VWF activity and factor VIII levels should be measured and repeated after delivery, or if labour is prolonged. ✓

Tranexamic acid should be considered in combination with treatment for all those with VWF activity less than 0.5 iu/ml, or as sole therapy for those with levels above 0.5 iu/ml if clinically indicated. This can be given orally or intravenously, and can be started prior to delivery. ✓

Platelet transfusions, as well as VWF factor replacement, may sometimes be required in type 2B VWD. D

The mode of delivery should be guided by obstetric indications. Spontaneous labour and normal vaginal delivery should be permitted if there are no other obstetric concerns, to minimise risk of intervention. ✓

For fetuses at risk of having type 2 or 3 VWD, FBS, external cephalic version, fetal scalp monitoring, ventouse delivery and midcavity forceps should be avoided. ✓

Recovery and half-life of factor VIII and VWF:RCo varies among patients and within individuals in different clinical settings. Delivery can be associated with rapid consumption of factor VIII and VWF, and the half-life can be reduced in the immediate postpartum.

Tranexamic acid, 1 g intravenously, may be helpful for low, normal VWF:RCo levels where VWF-containing concentrates are not thought necessary. It can also be given in conjunction with VWF concentrate and DDAVP.

Severe thrombocytopenia can occur in patients with type 2B VWD due to a rise in the abnormal VWF during pregnancy, and enhancing platelet binding and clearance. This can further aggravate the bleeding risk.[116] Platelet transfusions may therefore be required to maintain platelet count above 50×10^9/litre.[84,85]

Evidence level 3

Although VWF levels are normally elevated at birth, neonates with type 2, type 3 and more severe forms of type 1 disease will have reduced levels of VWF with or without factor VIII and may be at increased risk of both ICH and ECH.[97,98]

Evidence level 4

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5.5 *How can analgesia and anaesthesia be safely managed?*

For patients with type 1 VWD, where VWF activity has been normalised by pregnancy or treatment, central neuraxial anaesthesia can be offered. ✓

For patients with type 2 disease, central neuraxial anaesthesia should be avoided unless VWF activity is more than 0.5 iu/ml and the haemostatic defect has been corrected; this may be difficult to achieve in type 2 and central neuraxial anaesthesia should not be given in cases of type 3. ✓

For patients with type 2N VWD, central neuraxial anaesthesia should be avoided unless factor VIII level is more than 0.5 iu/ml. ✓

Prior to delivery, all women should be given the opportunity to discuss analgesia with a senior obstetric anaesthetist. ✓

In patients where an epidural catheter has been placed, consideration should be given to the need for repeat treatment prior to catheter removal, as the risk of bleeding is no less than with insertion. D

Intramuscular injections and postnatal nonsteroidal anti-inflammatory drugs (NSAIDs) are only suitable in the short term when VWF activity and factor VIII are more than 0.5 iu/ml. ✓

Central neuraxial anaesthesia (spinal and epidural) can be regarded as safe in women with type 1 VWD when VWF activity is greater than 0.5 iu/ml. In type 2 and 3 VWD, haemostasis in theory may not normalise even with replacement therapy because of associated platelet dysfunction.[117] While general anaesthesia may be seen as safer from the point of view of the bleeding risk, it poses significant additional risks and a risk/benefit analysis is required for these patients, involving a senior obstetric anaesthetist.

Indwelling catheters should generally be avoided, but where used, additional treatment should be considered for catheter removal, as the risk of bleeding is no less than at catheter insertion.[66,118]

Evidence level 4

Intramuscular injections should be avoided in patients with low levels of VWF:RCo or factor VIII as painful intramuscular haematomas may occur unless haemostatic support is provided. NSAIDs affect platelet function and can contribute to the bleeding tendency.

5.6 *What is the postpartum management?*

It is important to ensure that VWF activity and factor VIII levels are maintained at more than 0.5 iu/ml for at least 3 days following uncomplicated vaginal delivery and at least 5 days following instrumental delivery or after caesarean section. Management should be guided by results of laboratory investigations. ✓

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Women with VWD should be considered for tranexamic acid for the postpartum period. A standard dose is 1 g three to four times a day for 7–14 days. In some cases, prolonged administration for 2–3 weeks or more may be necessary. ✓

If thromboprophylaxis is indicated, low-molecular-weight heparin (LMWH) may be given to inpatients with adequate correction of VWF:RCo and factor VIII levels. When pharmacological thromboprophylaxis is contraindicated, mechanical methods should be employed. ✓

Women with VWD should be made aware of the risk of delayed bleeding and be encouraged to report excessive bleeding. For women with more severe cases, haemoglobin should be monitored and regular contact with the patient maintained for several weeks. Patients with type 3 VWD may require treatment with VWF concentrate for 2–3 weeks or even longer following delivery. ✓

The risk of postpartum bleeding is significant in women with VWD and can persist for several weeks. The pregnancy-induced increase in factor VIII and VWF is maintained in the first 48 hours after delivery, but VWF levels start to decline on day 3 post delivery.[91] In normal pregnancies, the median duration of bleeding after childbirth is 21–27 days, with delayed or secondary PPH occurring in less than 1% of cases. In women with VWD, this is much more common, affecting 20–25% of cases. The average time of presentation with PPH in women with VWD is 10–20 days after delivery.[88,89,119] Evidence level 4

For patients with significantly low prepregnancy levels of VWF, DDAVP should be considered in known responders. For type 2 and 3 disease, or severe type 1, care should be taken to ensure that VWF and factor VIII activity levels are maintained at more than 0.5 iu/ml for at least 3 days following vaginal delivery or 5 days after caesarean section. If the bleeding risk is prolonged by complicated delivery and delayed recovery, or development of sepsis, normal levels should be maintained for longer. This should be achieved by repeated administration of coagulation factor concentrates with regular monitoring of VWF and factor VIII levels.

Tranexamic acid can be used during the puerperium. A limited quantity is secreted in breast milk, but is unlikely to produce an antifibrinolytic effect in the infant.[63,120] Evidence level 3

Thromboprophylaxis is sometimes indicated if women have other risk factors for venous thromboembolism. While VWF and factor VIII levels are maintained in the normal range, women may be considered for prophylactic LMWH if indicated. Heparin should be avoided if VWF level or factor VIII level is less than 0.5 iu/ml.

Follow-up is important as many women may accept heavy vaginal bleeding as normal and do not report it. Telephone contact should be maintained with the patient and a follow-up haemoglobin considered at 2 weeks postpartum.

The combined contraceptive pill is useful for these women in the postpartum period for hormonal reduction in bleeding as well as increasing VWF production. It can be used postpartum if not breastfeeding,[121] with or without tranexamic acid.

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5.7 *What is the neonatal management?*

A plan for the diagnostic testing of the neonate following delivery, including cord blood sampling, should be included in the maternal pregnancy management plan. ✓

Cord blood samples for VWF activity should be taken for babies at risk of type 2 and 3 VWD. ✓

For neonates at risk of type 2 or 3 VWD, vitamin K should be given orally, unless VWF activity is shown to be normal. D

Neonates with type 3 VWD should be considered for routine cranial imaging prior to discharge and for short-term prophylaxis, with factor concentrate, if there has been significant potential trauma at delivery. D

In normal neonates, VWF antigen and activity levels are usually elevated at birth.[96] Diagnosis of mild VWD is therefore likely to be difficult in the neonatal period as mild conditions can be masked. Testing is usually deferred until around 6 months of age unless there are clinical bleeding issues. It is, however, usually possible to diagnose more severe type 2 and type 3 disease in this age group, and a cord sample should be obtained for factor VIII, VWF activity and antigen assays. All results should be interpreted against age-adjusted normal ranges. Referral for follow-up testing should be arranged prior to discharge.

Neonates with type 3 VWD will have very low/undetectable levels of factor VIII and VWF, and may be at increased risk of ICH although the incidence of this complication is poorly defined. Neonates with reduced VWF activity may also be at risk of muscle bleeds following intramuscular injection and should receive vitamin K orally.[97]

Evidence level 4

6. Factor XI deficiency

6.1 *What is the inheritance?*

Factor XI deficiency is an uncommon autosomal disorder which has both recessive and dominant inheritance patterns. B

The incidence in the non-Jewish population is 1/1 000 000; it is common in Ashkenazi Jews with heterozygosity in 8% and homozygosity in 0.2–0.5%. A

Clinicians should be aware that there is intra- and inter-individual variation in bleeding phenotype. D

Factor XI is a glycoprotein that plays a role in the amplification of the coagulation process after the initial production of thrombin. Factor XI deficiency is a bleeding disorder with an autosomal inheritance. The inheritance pattern is complex, with both dominant and recessive inheritance patterns described. However, some heterozygotes demonstrate a bleeding tendency.[122,123]

Evidence level 2++

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Severe factor XI deficiency is rare in the general population with an incidence of 1/1 000 000.[124] However, it is common among the Jewish population, especially Ashkenazi Jews. In this population, the heterozygous form occurs in 8–9%[125] and homozygosity in 0.2–0.5%.[126,127]

Evidence level 1+

Clinicians should be aware that clinical phenotypes vary even among individuals with the same factor level. In part, this may be due to differences in platelet function and levels of VWF.[128,129] The bleeding tendency can also be variable in the same individual, in response to different haemostatic challenges. The bleeding risk is highest if surgery or trauma involves sites of increased fibrinolysis. This relates to the antifibrinolytic role of factor XI, through the activation of thrombin activatable fibrinolysis inhibitor.[130]

Evidence level 3

6.2 *What are the different phenotypes?*

Plasma levels of factor XI show poor correlation with bleeding symptoms.

B

Spontaneous bleeding is rare, even with very low factor XI levels. However, these patients are often at risk of bleeding following surgery or trauma.

C

Heterozygotes have mild or moderate reduction in factor XI levels (more than 0.15–0.20 iu/ml). Most are asymptomatic, but patients with even mild reductions in factor XI (0.5–0.7 iu/ml) may have a bleeding tendency.

C

The clinical phenotype in factor XI deficiency is heterogeneous. There is a poor correlation between factor level and bleeding tendency;[129] however, Peyvandi et al.[131] demonstrated a weak correlation between factor XI level and clinical phenotype from data collected via the European Network of Rare Bleeding Disorders registry. Patients who suffered severe bleeding had a factor XI activity range of 0.09–0.41 iu/ml, while asymptomatic cases had levels between 0.14 and 0.39 iu/ml.

Evidence level 2+

Patients with homozygosity or compound heterozygosity have factor levels of less than 0.15–0.20 iu/ml. Although these are classed as severely deficient, spontaneous bleeding is rare. Bleeding usually occurs after surgery and trauma, especially when the site is rich in fibrinolytic activity, such as the oral and nasal mucosa, and genitourinary system.[132] Many patients with severe reduction in factor XI level do not have a bleeding tendency.[133,134]

Evidence level 3

Heterozygotes have mild to moderate reduction in factor XI level (levels between 0.15 and 0.70 iu/ml).[129] Some laboratories may quote an upper limit of 0.5 iu/ml, but cases with bleeding tendency have been described in individuals with levels between 0.5 and 0.7 iu/ml.[129]

Evidence level 2+

6.3 *What are the risks in pregnancy to mother and baby?*

Factor XI does not usually increase during pregnancy; however, levels should be checked at booking, in the third trimester and prior to invasive procedures.

C

Women with factor XI deficiency may suffer excessive bleeding after miscarriage or termination, especially if they have a bleeding phenotype.

C

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There is increased risk of PPH in factor XI-deficient women, which is highest in those with a bleeding phenotype and of blood group O, and least in non-O blood groups with a nonbleeding phenotype. C

Patients with factor XI deficiency should be assessed for the presence of other potentially compounding factors, such as low VWF levels and platelet dysfunction. C

No special precautions for the baby are required for delivery unless the neonate is at risk of homozygosity or compound heterozygosity. D

There are reports of increased levels of factor XI in pregnancy. Factor XI level should be checked in the third trimester or prior to invasive or surgical procedures.[135]

The risk of miscarriage does not appear to be increased, however, women may suffer excessive bleeding after miscarriage or termination. The risk is particularly increased in those women with a bleeding phenotype.[90,136]

The risk of PPH is increased in factor XI-deficient women, in both homozygotes (17–30%)[137] and heterozygotes, with an overall risk of 16–22%.[136,138] This risk is increased in those with a bleeding phenotype, with a relative risk of 7.2 (95% CI 1.99–25.90).[136,138] A 2015 study suggests that having blood group O increases the risk of PPH; those with blood group O had nearly a five-fold increased risk compared with the non-O group (26.4% versus 6.3%); those with blood group O and 'bleeding' phenotype had the highest risk with 32.8% of women having a PPH. Women with non-O blood group and nonbleeding phenotype, in contrast, had the lowest risk at 5.7%, i.e. near-normal PPH risk.[139] Evidence level 2+

It is likely that other clotting factors, such as levels of VWF, and platelet function may play a role in determining the bleeding tendency or otherwise in factor XI-deficient patients. Therefore, other relevant clotting factors should be measured to help assess bleeding tendency.[128]

There are no reports of spontaneous bleeding or ICH in neonates. PND is not necessary as the morbidity with factor XI deficiency is low. Haemorrhage due to peripartum events is rare, but trauma to the head should be avoided if there is risk of homozygosity or compound heterozygosity. Neonatal factor XI level is approximately half that of adult levels.[96] If the child is a male and circumcision is planned, a sample should be taken to help direct management for this. Mild factor XI deficiency cannot be reliably diagnosed until after the first few months. Evidence level 3

6.4 *What are the therapeutic options?*

Treatment options include tranexamic acid, factor XI concentrate and fresh frozen plasma (FFP), however, women with a nonbleeding phenotype or unknown status can often be managed expectantly. C

Tranexamic acid should not be given simultaneously with prophylactic factor XI concentrate as this is considered to increase thrombotic risk. For many women, it is likely that tranexamic acid alone will be sufficient to prevent PPH. D

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If FFP is given to raise factor XI levels, solvent detergent (SD)-FFP should be used when available. D

Recombinant factor VIIa is not licensed for this condition and is generally not recommended, except if there is an inhibitor to factor XI. D

Treatment options include tranexamic acid, factor XI concentrate and FFP.[132,134] Issues with factor XI concentrate are the risk of thrombosis and (rarely) inhibitor development in patients with very low factor XI levels. Reports of thrombosis were originally published in the 1990s[140,141] and guidelines on restricting dose to prevent the level rising above lower levels of 0.7 iu/ml were established. More recently, lower doses have been recommended, as some individuals still had thrombotic events.[142] As this is a blood product, there is also the very rare risk of transfusion-transmitted infection or allergic reactions. Low-dose recombinant activated factor VIIa has been used successfully in patients with severe factor XI deficiency undergoing surgery.[143] It avoids the need for plasma derived products, but as yet, there is insufficient evidence to make a recommendation for its use. Evidence level 2–

Factor XI inhibitors may occur after factor XI replacement in cases with homozygous factor XI deficiency. One study demonstrated inhibitor antibodies in 7 of 188 cases, all of whom had the same genetic defect,[144] which suggests that the risks and benefits of factor XI treatment need to be carefully assessed. Low-dose recombinant activated factor VIIa with tranexamic acid has been shown to be haemostatically effective during surgery in factor XI deficient patients with inhibitors[145] and in one case, activated prothrombin complex concentrate was given to cover caesarean delivery.[146] Evidence level 3

Most women can be managed with tranexamic acid alone, but where prophylactic factor XI is required, concomitant use of tranexamic acid should be avoided.[147] Evidence level 4

FFP contains variable amounts of factor XI, but commercially available SD-FFP has less variation than single donor methylene blue-treated FFP and a mean factor XI activity of 0.7–0.9 iu/ml. Transfusion-transmitted infection or allergic reactions are possible in addition to risk of thrombosis or inhibitor development in homozygotes.[123] Evidence level 3

Off-label recombinant factor VIIa has been used occasionally, especially if an inhibitor is present.[143] However, as the effect cannot easily be measured, the safe dose is unknown and it has been associated with thrombosis.[148] Evidence level 4

One study reports development of a protocol used perioperatively for five procedures in patients with inhibitors using tranexamic acid from 2 hours preoperatively until 7–14 days postoperatively in addition to a single infusion of low-dose recombinant factor VIIa.[145] Evidence level 3

6.5 What is the antenatal, intrapartum and postpartum management?

Factor XI or tranexamic acid is not usually required antenatally unless an invasive procedure is undertaken or if there is bleeding following miscarriage or surgical procedure. C

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Delivery plans need to be individualised. Prophylactic factor XI replacement should be considered if homozygous/compound heterozygous, previous history of PPH or general bleeding history. Otherwise, management can be expectant, with tranexamic acid alone and factor replacement reserved for excess bleeding. C

There is no increased risk of antenatal bleeding or spontaneous miscarriage with factor XI deficiency.[136,138]

Due to the unpredictable nature of bleeding and the likely unchanged factor XI level during the pregnancy, treatment plans around labour and delivery need to be individualised. Factors to be considered are: personal history of bleeding (a standardised bleeding assessment tool is helpful to assess phenotype),[101] family history of bleeding, mode of delivery, previous obstetric history, blood group and factor XI level if very low (less than 0.1–0.2 iu/ml). Some authors suggest that prophylactic treatment for all modes of delivery should be given for patients with homozygous or compound heterozygous disease,[149] while others argue that factor replacement is not mandatory. In a retrospective study in 2005, Salomon et al.[137] studied outcome in 62 women with severe factor XI deficiency. Overall, 43 women in 93 deliveries had no PPHs (69.4%); eight of which were caesarean sections. Haemorrhage occurred in 19 deliveries; 17 of which occurred in six women. They concluded that treatment could be reserved for those that demonstrate a bleeding tendency. Evidence level 3

6.6 *Can central neuraxial anaesthesia be given?*

Central neuraxial anaesthesia should not be given to women with low factor XI levels with a known bleeding phenotype, where the phenotype is not clear or when there is a severe reduction in level. In those with a nonbleeding phenotype, discussion and counselling should be given regarding the risks and benefits of allowing neuraxial anaesthesia with or without factor replacement. ✓

Results of retrospective studies[138,139] do not suggest an increased risk of bleeding with the use of regional block in women with factor XI deficiency. However, there is an extremely low risk in the general population and these small studies are not powered to demonstrate if there is an increase in risk in the factor XI-deficient population. The risks and benefits need to be discussed on an individual basis. Where there is a clear nonbleeding phenotype, the balance of risks may be in favour of use of central neuraxial anaesthesia, especially if via a single pass spinal injection. However, due to its rarity and variable bleeding tendency where there is a clear or possible personal bleeding history (i.e. in those women who have not had an invasive procedure to establish whether they have a bleeding phenotype), central neuraxial anaesthesia should be withheld or prophylaxis given to raise the factor XI level. Reports with adequate replacement suggest that this is safe in preventing spinal haematoma.[150,151] Again, however, these studies are very small and not powered to detect a difference in the incidence of bleeding with central neuraxial anaesthesia. Evidence level 3

7. Rare bleeding disorders

7.1 *What are they?*

Clinicians should be aware that rare bleeding disorders include inherited deficiencies of fibrinogen, factors II, V, VII, X, XI and XIII, combined factor V and factor VIII (factor V+VIII) deficiencies, and congenital deficiency of vitamin K-dependent factors. D

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Rare bleeding disorders have been defined as monogenic bleeding disorders caused by deficiency of a soluble coagulation factor (or factors) other than VWD and haemophilia A or B.[122,152] They represent 3–5% of all inherited coagulation deficiencies and include inherited deficiencies of fibrinogen, factors II, V, VII, X, XI and XIII, combined factor V+VIII deficiencies, and congenital deficiency of vitamin K-dependent factors. Factor XI and fibrinogen deficiency are discussed in separate sections 6 and 8. The evidence to support the majority of statements is weak and recommendations are derived from expert opinion with reference to small published retrospective case series and open label observational studies.[123,131] Such data are also subject to ascertainment bias and may overestimate the severity of bleeding attributable to specific factor levels. Recommendations made in this guideline are consistent with the current British Society for Haematology guidelines on rare coagulation disorders.[123]

Evidence level 4

7.2 *What is the inheritance of factors II, V, VII, X and XIII, and combined factor V+VIII deficiencies?*

Genetic counselling should be provided, with the understanding that most rare inherited bleeding disorders are autosomal recessive in inheritance and heterozygote carriers are usually asymptomatic. For affected women or asymptomatic heterozygous carriers, consanguinity should be established to allow counselling, screening when possible and formulation of a delivery plan for a potentially affected baby.

D

The prevalence of severe deficiency (homozygous or compound heterozygous) in the general population ranges from approximately 1 in 2 000 000 for factor II and XIII deficiency, 1 in 1 000 000 for factor V, X and V+VIII deficiency and 1 in 500 000 for factor VII deficiency.[122] The prevalence is higher in areas with high consanguinity rates. Heterozygotes (parents and children of the probands) often have approximately half-normal levels of coagulation factors and are usually asymptomatic[122,153,154] although some authors suggest that there may be an increase in bleeding symptoms in carriers.[155,156] Babies at risk of homozygosity or compound heterozygosity are at significant risk of bleeding following delivery, including ICH.[122,131]

Evidence level 4

7.3 *What are the risks in pregnancy to mother and baby, and what are the treatment options?*

Clinicians should appreciate that coagulation factor levels can change during pregnancy. However, this is unlikely to influence haemostasis in women with severe deficiency. Management should take into account both the factor level and whether there is a clinical history of bleeding.

C

Treatment plans may need to be modified according to the nature of individual bleeds or procedures, and to the background bleeding phenotype of each case. Factor replacement therapy is usually advised for delivery in women with severe coagulation factor deficiency and/or a bleeding history. Tranexamic acid at a dose of 15–20 mg/kg or 1 g four times daily alone can be used for minor bleeds and in combination with factor replacement.

D

If the baby is at risk of severe deficiency, the delivery plan should include avoidance of ventouse, midcavity forceps, FBS and FSE.

✓

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Central neuraxial anaesthesia, postpartum pharmacological thromboprophylaxis and NSAIDs should usually be avoided in women with severe deficiencies as it may be difficult to guarantee consistent normalisation of haemostasis even after treatment. They may be used after individual assessment if adequate replacement therapy is confirmed. ✓

The association between coagulation factor activity level and clinical bleeding severity is more apparent for factor X, factor XIII and combined factor V+VIII deficiencies, with a weaker association for factor V and factor VII deficiencies.[131] Factor VII and X levels increase during pregnancy, but levels usually remain insufficient for haemostasis in severely affected cases.[157,158] Factor II and factor V do not increase during pregnancy;[87,159] factor XIII decreases during normal pregnancy.[160]

If available, specific recombinant or virally inactivated plasma-derived factor concentrates should be used in preference to FFP or cryoprecipitate.[123] Tranexamic acid may be useful alone for minor bleeds or as an adjunct to replacement therapy without significantly increasing the risk of thrombosis.[161] Where treatment is given, it should be in established labour or prior to caesarean section.

Evidence level 3

Assisted vaginal delivery and invasive fetal monitoring is not normally contraindicated for neonates expected to be heterozygous carriers of these rare bleeding disorders as there is insufficient evidence from case reports to justify restricting these helpful aids to delivery. Heterozygous individuals commonly do not manifest a bleeding tendency[122,154] although this may not be the case for factor VII deficiency where 2% of patients with a severe bleeding phenotype are heterozygotes.[162] If there is a risk of a severely affected neonate (homozygous or compound heterozygous), full restrictions are required (as per severe haemophilia) (see Appendix IV).

Evidence level 4

Central neuraxial anaesthesia, pharmacological thromboprophylaxis and NSAIDs should usually be avoided unless confident that normal haemostasis is achieved. When a factor concentrate is available and adequate factor levels are maintained, these interventions can be considered on a case-by-case basis with specialist input and appropriate laboratory monitoring.

Prothrombin (factor II) deficiency

If factor II activity is less than 0.2 iu/ml and there is significant bleeding, established labour or prior to caesarean section, give prothrombin complex concentrate 20–40 iu/kg to achieve factor II activity 0.2–0.4 iu/ml. Consider further prothrombin complex concentrate 10–20 iu/kg at 48-hour intervals to maintain factor II activity more than 0.2 iu/ml for at least 3 days. Women already receiving prophylactic prothrombin complex concentrate can continue it throughout pregnancy. D

Case reports have described associations among factor II deficiency and antepartum haemorrhage (APH), pregnancy loss and PPH.[163,164] Some women may already be on prophylaxis with prothrombin complex concentrate to maintain factor II trough levels of more than 0.1 iu/ml, which can continue during pregnancy. Minor bleeds can be managed with tranexamic acid, 1 g four times a day. Management with prothrombin complex concentrate, 20–40 iu/kg during labour, is recommended aiming to maintain factor II activity more than 0.2 iu/ml for at least 3 days.[123,163]

Evidence level 3

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Factor V deficiency

For significant bleeding or delivery in women with factor V activity less than 0.2 iu/ml, 15–25 ml/kg FFP should be considered once in established labour or before caesarean section to achieve factor V activity 0.2–0.4 iu/ml with further FFP 10 ml/kg at 12-hour intervals to maintain factor V activity more than 0.2 iu/ml for at least 3 days. Where possible, SD-FFP should be used to reduce infective risk. D

For severe bleeding or caesarean section, consider additional platelet transfusion. D

Factor V deficiency has been associated with PPH.[165,166] Cases have been described of patients with factor V activity more than 0.1 iu/ml and severe bleeding, therefore, clinical history (for example, using the International Society on Thrombosis and Haemostasis bleeding assessment tool)[101] should be considered in addition to laboratory levels. Peyvandi et al.[131] identified a factor V level for asymptomatic patients of 0.12 iu/ml (95% CI 0–0.34). There is currently no factor concentrate available, so treatment with a pathogen-reduced FFP (e.g. SD-FFP) has been recommended.[167] For minor bleeding, tranexamic acid can be used, however, for more significant bleeding or delivery in women with severe factor V deficiency, SD-FFP has been used successfully. Recombinant factor VIIa has also been used off label, for example, in patients with FFP allergy.[168,169] Evidence level 3

Platelet concentrates have been used as an additional source of factor V in combination with SD-FFP.[170]

Severe factor VII deficiency

For factor VII activity less than 0.2 iu/ml in the third trimester with prior history of bleeding, consider recombinant factor VIIa 15–30 micrograms/kg every 4–6 hours for at least 3 or 5 days following caesarean section. For all other women, recombinant factor VIIa 15–30 micrograms/kg is recommended only in response to abnormal bleeding. For mild bleeding, tranexamic acid (15–20 mg/kg or 1 g four times daily) can be used. For severe bleeding, recombinant factor VIIa 15–30 micrograms/kg can be given and repeated if required every 4–6 hours, usually for a minimum of three doses. D

Mild asymptomatic factor VII deficiency is not uncommon and is usually identified because of an isolated abnormal prothrombin time.[155,171] In addition, it does not require any treatment or restrictions in pregnancy although severe bleeding is more likely with factor VII levels less than 0.01 iu/ml.[172] Data from the European Registry of Rare Bleeding Disorders identified a factor level between 0.15 and 0.35 iu/ml for asymptomatic patients, however, the correlation of factor level with bleeding was weak.[131] A bleeding history appears more predictive of further bleeding than the factor VII level.[173] APH, PPH and pregnancy loss have been reported,[156,174,175] however, women with no history of bleeding do not appear to be at increased risk of PPH.[176] Evidence level 3

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Severe factor X deficiency

For delivery in women with factor X activity less than 0.3 iu/ml in the third trimester who have a history of bleeding and all those who require caesarean section, use prothrombin complex concentrate 20–40 iu/kg (or factor X concentrate if available) to achieve factor X activity more than 0.4 iu/ml. Consider further prothrombin complex concentrate 10–20 iu/kg once daily to maintain factor X activity more than 0.3 iu/ml for at least 3 days. Antenatal prophylaxis may be considered in women with a history of recurrent bleeding or adverse pregnancy outcome using prothrombin complex concentrate 20–30 iu/kg two or three times a week to maintain trough factor X more than 0.01 iu/ml.

D

APH, pregnancy loss and PPH have been described in patients with factor X deficiency.[177,178] Prophylaxis with replacement therapy has been used antenatally for women with previous adverse pregnancy outcomes.[179] Reported replacement regimens have been variable and we have made recommendations consistent with the UKHCDO guidelines on the management of rare bleeding disorders.[123] If a licensed factor X concentrate is available, then this could be used as an alternative to a prothrombin complex concentrate.

Evidence level 3

Severe factor XIII deficiency

During pregnancy, increased intensity prophylaxis is required using factor XIII plasma concentrate or recombinant factor XIII (if A-subunit deficiency). Dosing frequency should be increased from every 28 days to every 14–21 days to maintain factor XIII more than 0.2 iu/ml. For delivery, consider additional factor XIII concentrate 10–40 iu/kg once in established labour or before caesarean section, depending on the interval since last prophylaxis.

D

Severe factor XIII deficiency is associated with bleeding and a high rate of pregnancy loss without treatment.[180] Long-term prophylaxis with factor XIII concentrate is recommended in all cases of severe deficiency with a personal or family history of bleeding,[123] with either a plasma-derived[181] or recombinant factor XIII concentrate in patients with A-subunit deficiency.[182] Prophylaxis should be continued and intensified in pregnancy to reduce the risk of pregnancy loss and PPH.[160,183] Although there has been a suggestion that heterozygous carriers may experience trauma-related bleeding,[156] this has not been studied systematically and there is evidence that maintaining levels of 0.03–0.10 iu/ml can be sufficient to prevent bleeding in severely affected patients.[184,185]

Evidence level 3

Factor V+VIII deficiency

For delivery in women with combined factor V+VIII deficiency, if factor V activity less than 0.2 iu/ml in the third trimester, consider SD-FFP 15–25 ml/kg once in established labour or before caesarean section to achieve factor V activity 0.2–0.4 iu/ml. Consider further SD-FFP 10 ml/kg once every 12 hours to maintain factor V activity more than 0.2 iu/ml for at least 3 days. Consider additional recombinant factor VIII if the factor VIII activity is less than 0.5 iu/ml in the third trimester.

D

Combined factor V+VIII deficiency has been associated with PPH.[186,187] Factor VIII levels, but not factor V levels, increase in pregnancy.[87,188] Various treatment strategies have been used in pregnancy, including recombinant factor VIII alone, or combinations of FFP, recombinant factor VIII and DDAVP.[123,188]

Evidence level 4

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8. Fibrinogen disorders

8.1 *What is the nature and inheritance of afibrinogenaemia, hypofibrinogenaemia and dysfibrinogenaemia?*

Clinicians should be aware that fibrinogen disorders can be autosomal recessive (afibrinogenaemia) or autosomal dominant (with quantitative and/or qualitative defects) and are associated with a variable clinical phenotype. D

Severe fibrinogen deficiency (afibrinogenaemia) is an autosomal recessive disorder and is associated with mild-to-severe bleeding and has a prevalence of 1/1 000 000.[122,131,189,190] Partial quantitative (hypofibrinogenaemia), with or without qualitative defects (dysfibrinogenaemia), can be autosomal dominant in inheritance and may be asymptomatic or associated with a variable risk of bleeding and/or venous and arterial thrombosis.[191–194] Poor wound healing and splenic rupture have also been reported with severe and partial fibrinogen deficiency.[193] Laboratory diagnosis of afibrinogenaemia is straightforward, but diagnosis of hypofibrinogenaemia and dysfibrinogenaemia may be unreliable in the neonate, requiring retesting in later life.[123] Evidence level 4

8.2 *What are the risks in pregnancy to mother and baby?*

Clinicians should be aware that severe fibrinogen deficiency may be associated with bleeding, but quantitative and qualitative deficiency can also be associated with thrombosis and pregnancy loss. D

Afibrinogenaemia, hypofibrinogenaemia and dysfibrinogenaemia have been variably associated with APH, PPH, venous thrombosis and pregnancy loss.[175,195–197] In the neonate, afibrinogenaemia has been associated with ICH and umbilical bleeding.[189,198] Although fibrinogen levels increase during pregnancy,[87] this does not necessarily protect against complications. Evidence level 3

8.3 *What is the management of pregnancy and delivery?*

If functional fibrinogen is less than 0.5 g/litre, consider prophylaxis throughout pregnancy with fibrinogen concentrate initially 50–100 mg/kg twice per week, adjusted to maintain trough fibrinogen activity more than 1 g/litre. Higher doses of fibrinogen concentrate are likely to be required to maintain fibrinogen activity as pregnancy progresses. Consider additional fibrinogen concentrate for established labour to ensure fibrinogen activity more than 1.5 g/litre for at least 3 days. Tranexamic acid can be used for minor bleeding. D

Because of the variable clinical phenotype associated with hypofibrinogenaemia and dysfibrinogenaemia, a personal and/or family history is required for management decisions. If there is no personal or family history of bleeding or thrombosis, expectant management is recommended for pregnant women or the neonate. D

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Fibrinogen replacement therapy is associated with a high risk of thrombosis and requires vigilance. Pregnant women with a thrombotic phenotype or other risk factors for venous thrombosis, and with a low risk of bleeding, should be considered for thromboprophylaxis with LMWH. ✓

Central neuraxial anaesthesia, NSAIDs and intramuscular injections should generally be avoided for women with severe fibrinogen deficiency, or a personal or family history of bleeding, due to the difficulty in assuring correction with factor concentrate. They may be used after individual assessment if adequate replacement therapy is confirmed. ✓

The use of midcavity forceps, rotational forceps, ventouse, FBS and FSE should be avoided in a baby at risk of fibrinogen deficiency associated with a bleeding phenotype. ✓

Plasma-derived fibrinogen concentrate is recommended for treatment or prevention of bleeding in severe cases[123] although tranexamic acid is an option for minor bleeding. If fibrinogen concentrate is not available, cryoprecipitate can be used.[190] Antenatal prophylaxis with fibrinogen replacement therapy is recommended for severe fibrinogen deficiency (for reducing the risk of bleeding and pregnancy loss) and there is evidence of better outcomes if started preconception.[164] Higher doses of fibrinogen concentrate are likely to be required to maintain fibrinogen activity as pregnancy progresses.[197,199] Additional fibrinogen concentrate should be considered for established labour to ensure fibrinogen activity more than 1.5 g/litre for at least 3 days.[123] Continuous infusion is an option to minimise peaks and troughs.[199]

Women with dysfibrinogenaemia can experience similar pregnancy complications to women with hypofibrinogenaemia. There are isolated case reports suggesting that these may be prevented by fibrinogen replacement throughout pregnancy.[196,200] Case reviews have highlighted that dysfibrinogenaemia is often asymptomatic.[191,192,194] Evidence level 3

Thrombotic complications are very common in patients with congenital fibrinogen deficiency, with or without fibrinogen replacement therapy.[198] LMWH prophylaxis has been used both antenatally and postpartum.[200,201]

Fibrinogen replacement therapy does not necessarily prevent all pregnancy complications,[198] possibly due to difficulty maintaining adequate trough levels.

Severe fibrinogen deficiency is associated with a risk of neonatal ICH.[164,189] Evidence level 4

9. Platelet function disorders

Clinicians should be aware that the spectrum of bleeding in patients with platelet function disorders varies and may first present in pregnancy. D

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Women known to have a platelet dysfunction disorder should receive prepregnancy counselling from a multidisciplinary specialist team with expertise in caring for patients with platelet function disorders. ✓

There is a variety of disorders of platelet function, giving rise to mucocutaneous bleeding. The most severe conditions include Glanzmann's thrombasthenia (GT) and Bernard Soulier Syndrome (BSS), caused by deficiency of functioning integrins, GP IIb/IIIa or Ib, respectively. Bleeding severity ranges from minor bleeds to potentially fatal haemorrhages and differs among affected individuals, even within the same family.[202,203] Evidence level 4

Pregnancy and childbirth present significant haemorrhagic risks and require careful management. Women should be informed of their risk before becoming pregnant.[204] Evidence level 3

9.1 Bernard Soulier Syndrome (BSS)

9.1.1 What is the aetiology?

Clinicians should be aware that BSS is caused by genetic abnormality of an important platelet adhesion receptor (GP Ib-IX-V receptor) and is often associated with a severe bleeding phenotype. ✓

BSS is caused by quantitative or qualitative deficiency of the membrane GP Ib-IX-V complex, leading to abnormal adhesion of platelets. More than 30 genetic mutations have been identified, determining various severities of bleeding.[205] Bleeding often starts in childhood with oral bleeding and epistaxis, but patients may be first diagnosed in pregnancy. Menorrhagia is common and can be challenging to manage.[202] BSS is associated with thrombocytopenia and large platelets, and could be confused with immune thrombocytopenic purpura, particularly as the platelet count can be as low as less than 30×10^9/litre and can vary in the same individual.[202] Evidence level 3

9.1.2 What is the inheritance?

BSS is an autosomal recessive disorder. In areas of high consanguinity, it may be prudent to test the father using platelet flow cytometry for GP Ib surface density. ✓

BSS is mainly inherited as an autosomal recessive trait; heterozygosity is usually asymptomatic. The fetus of an affected mother will be heterozygous providing the father is not a carrier. In areas of high consanguinity, it may be prudent to test the father using platelet flow cytometry for GP Ib surface density.[206] Evidence level 4

9.1.3 What are the maternal risks?

BSS is associated with significant risk of primary and secondary PPH, and wound haematoma. Management of delivery, therefore, requires careful planning with the multidisciplinary team. A

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Peripartum haemostatic management should be guided by assessment of the individual phenotype. D

Patients with a bleeding history should be given a platelet transfusion prophylactically at delivery or before caesarean section, in combination with tranexamic acid. Platelets should be human leucocyte antigen (HLA)-matched where possible to reduce the risk of alloimmunisation and platelet refractoriness. D

Tranexamic acid should be given at the onset of labour and continued regularly through the postpartum period until lochia is minimal. D

DDAVP has variable efficacy and is unlikely to be useful as sole therapy in BSS. D

Central neuraxial anaesthesia should be avoided. ✓

A systematic review of the literature identified reports of 30 pregnancies among 18 women. Primary PPH occurred in 33% and secondary in 40%. Two women had emergency hysterectomy and blood transfusion was required in 15.[207] Wound haematomas are also reported, in relation to caesarean section wound and perineal trauma.[208–210] Evidence level 2++

Depending on the individual bleeding phenotype, required treatment can range from expectant management only to prophylactic platelet transfusions in combination with intravenous tranexamic acid.[204]

There are few reports in the literature to guide the management of BSS in pregnancy, but case reports and mini case series show that prophylactic platelet transfusions are the treatment of choice in most cases. However, platelet transfusion is associated with risk of alloimmunisation and each platelet transfusion should be considered carefully.[211] Evidence level 4

Observational studies and case reports have demonstrated the successful use of tranexamic acid in the prevention and treatment of bleeding after vaginal delivery and caesarean section, with reduced amount of blood loss and requirement for transfusion.[71]

In some cases, there can be shortening of the bleeding time with DDAVP,[212,213] but the effect is not reliable and it is unlikely to be sufficient as sole therapy in the context of pregnancy. If used, attention should be given to fluid restriction for the ensuing 24 hours (see section 4.9).

Central neuraxial anaesthesia should be avoided in women with BSS even after treatment with platelets, due to the uncertain individual response to platelets and possibility of platelet refractoriness.

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9.2 *Glanzmann's thrombasthenia (GT)*

9.2.1 What is the aetiology?

Clinicians should be aware that GT is a disorder of platelet function with autosomal recessive inheritance and is often associated with severe bleeding tendency. ✓

GT is caused by lack of or nonfunctioning GP IIb/IIIa due to missense mutations in ITGA2B and ITGB3. Platelet–platelet aggregation is impaired, with defective primary haemostasis and clinical presentation in early childhood.

9.2.2 What are the maternal risks?

GT is associated with significant risk of intrapartum and PPH, and a careful plan of management is needed for women preparing for labour and delivery. B

HLA-matched platelet transfusions and/or recombinant factor VIIa should be given prophylactically, at delivery, for patients with a history of bleeding. Repeat doses may be required depending on the clinical picture. D

DDAVP has not been shown to be effective in GT and is unlikely to be helpful. ✓

Tranexamic acid should be given from the onset of established labour and continued regularly through the postpartum period until lochia is minimal. ✓

Central neuraxial anaesthesia should be avoided. ✓

A systematic review of 40 cases of GT in pregnancy, described in the literature, found antenatal bleeding in 50% of women, primary PPH in 34% and secondary PPH in 24%. While antenatal bleeding tended to be mild, postpartum bleeding was frequently severe and occurred up to 20 days after delivery, with a median time of 10 days.[214] Evidence level 2–

A systematic review[214] showed only partial success with prophylactic platelet transfusion prior to delivery, with PPH in 38% of treated women compared with 63% in women who had not received platelets. Platelets should be HLA-selected, starting with one to two adult doses and further doses depending on observed bleeding.

Recombinant factor VIIa is licensed for use in patients with GT who have antibodies to GP IIb/IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.[215] The recommended dosage is 90 micrograms/kg (range 80–120 micrograms/kg) by intravenous injection every 2 hours (range 1.5–2.5 hours). At least three doses should be administered to secure haemostasis in patients with active bleeding. Due to the low prevalence of patients with GT and platelet refractoriness, the clinical experience with this treatment is limited. The UKHCDO guideline from 2006 suggested that recombinant factor VIIa in combination with tranexamic acid may help to reduce the need for platelet transfusion,[204] however, in three case reports, it was not found to be successful.[214] Evidence level 3

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DDAVP has been tried in some patients with GT and may shorten bleeding time, but there is no notable clinical efficacy.[216] Tranexamic acid may be helpful as sole therapy and in combination with platelets for the prevention or treatment of bleeding.

Evidence level 4

Central neuraxial anaesthesia should be avoided in women with severe platelet function defects even after treatment with platelets due to the uncertain individual response to platelets and possibility of platelet refractoriness.

9.2.3 What are the risks to the fetus?

Maternal alloimmunisation to paternally-derived fetal platelet antigens (GP IIb/IIIa) may cause fetal thrombocytopenia and risk of ICH and other fetal bleeding.

B

If fetal-maternal alloimmunisation does not occur, there is no need to restrict aids to delivery.

✓

The necessity for platelet transfusions leads to a high prevalence of alloimmunisation against human platelet antigen or HLA epitopes, with platelet refractoriness and risk of fetal maternal alloimmunisation.[217] Of 40 pregnancies reviewed, three fetuses (7%) died from ICH between 24 and 31 weeks of gestation.[214] The risk is highest in women who have received multiple platelet transfusions, but may also occur in nontransfused women with absent expression of GP IIb/IIIa who develop antibodies when presented with paternally-derived fetal GP IIb/IIIa epitopes.

Evidence level 2++

If alloimmunisation does not occur, there is no need to restrict interventions during labour unless there is a suggestion of carrier status in the father or consanguinity, putting the baby at risk of severe disease.

9.2.4 What are the treatment options?

Women should be monitored for platelet-specific alloantibodies at booking, and at 28 and 34 weeks of gestation.

C

If fetal-maternal alloimmunisation occurs, management should involve a fetal medicine unit with experience of these conditions, and treatment with intravenous immunoglobulin with or without steroids should be considered.

D

Amniocentesis with platelet typing may be considered in cases of paternal heterozygosity.

✓

If the baby is at risk of homozygous GT or fetomaternal alloimmune thrombocytopenia (FMAIT), restrictions to delivery should be applied, as for all babies at risk of ICH. This includes avoidance of ventouse, midcavity forceps, FSE and fetal scalp sampling. Depending on risk, an elective caesarean section may be considered.

B

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Neonatal care of potential alloimmunisation requires a cord platelet count and withholding intramuscular vitamin K until the result is known, or administering it orally. A platelet count below the normal range should be repeated at day 3–5 when the platelet nadir is reached, due to development of the neonatal spleen. Platelet transfusion should be given if the platelet count is less than 30 × 10^9/litre. D

Women should be monitored for alloantibodies at booking, and at 28 and 34 weeks of gestation. Antibody titres are not currently measured as there is conflicting evidence for correlation with bleeding risk.[218,219] Increased fetal risk can be expected if the mother has platelet refractoriness or previous fetal thrombocytopenia. Evidence level 2+

There is no evidence to guide management of FMAIT in GT, but if alloimmunisation occurs, treatment with intravenous immunoglobulin with or without steroids should be considered, as for FMAIT unrelated to inherited platelet disorders.[220–222]

The zygosity of the father will indicate whether the risk to the baby is 50% or 100%, and amniocentesis with platelet typing may be considered in cases of paternal heterozygosity. This would need cover with platelet transfusion to avoid maternal bleeding. Antenatal FBS should be avoided because of bleeding risk to the mother or affected fetus.[223–225] Evidence level 4

The majority of cases of ICH associated with FMAIT occur in utero and early delivery by caesarean section is usual practice.[222] Evidence level 2++

Neonatal thrombocytopenia from FMAIT can result in painful muscle haematomas from intramuscular injections and vitamin K should be withheld until the diagnosis is excluded or given orally. Platelet transfusion should be given if the platelet count is less than 30 × 10^9/litre, or if bruising or bleeding is visible. Platelets should be ABO and rhesus D compatible, free from antibody and screened for cytomegalovirus. In babies with FMAIT, response is likely to be short lived due to circulating maternal antibody. Intravenous immunoglobulin may provide a more sustained response, but there is usually a delay of 24–48 hours before a satisfactory rise in platelet count is obtained.[226] Evidence level 4

9.3 Other congenital platelet function defects

9.3.1 What are the therapeutic options?

Women with mild platelet function disorders may require treatment to cover delivery. ✓

DDAVP and/or tranexamic acid can be used to cover delivery. D

Tranexamic acid should be continued postpartum until lochia is minimal. ✓

Central neuraxial anaesthesia should only be given if the risks are considered to be outweighed by the benefits and the haemostatic defect has been corrected. A platelet transfusion may be necessary beforehand and epidural catheter should not be left in situ. ✓

Patients with mild platelet function defects, such as storage pool disease, signalling defects or ADP receptor abnormality, do not usually bleed spontaneously, but require treatment during haemostatic challenges.

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Although DDAVP does not appear to have a direct effect on platelets, the increase in ultra large VWF multimers improves platelet adhesion and a good response is usually obtained with DDAVP in patients with mild platelet function defects.[216,227] DDAVP should be given in established labour, with platelets held in reserve if excess bleeding occurs. The antidiuretic effect of DDAVP requires that the patient be fluid restricted to 1 litre for 24 hours after administration.

Evidence level 3

For mild platelet dysfunction, if individual circumstances dictate that the risks of central neuraxial anaesthesia are outweighed by the benefits, spinal anaesthesia is preferred to epidural given its lower bleeding risk and immediate withdrawal. A platelet transfusion should be considered beforehand.

10. Management of women with inherited bleeding disorders who request termination of pregnancy

Women who have disorders with a medium or high bleeding risk (Appendix II) require multidisciplinary management in a unit with 24-hour access to blood products, factor replacement and specialist haematological advice. ✓

Factor levels should be measured in haemophilia carriers, women with VWD and women with known factor deficiencies (factor VII, X, XI and XIII) prior to medical or surgical termination. ✓

Factor levels should be corrected to those indicated for labour with the treatments outlined above and maintained for 24 hours post procedure. ✓

Bleeding post procedure should be closely observed as an inpatient and similar treatments outlined for post-natal management should be employed. ✓

In the days and weeks following the procedure, open access to gynaecology units and haemophilia centres must be arranged as the risk of bleeding can continue for several weeks. ✓

Many of the principles used to manage women during labour and the postpartum period are applied to this group of women. Early referral to specialised services is essential to optimise management in this patient group.

The majority of women requesting termination of pregnancy will be in the first or early second trimesters. Clotting factor levels will therefore be similar to nonpregnant levels and the increases observed in pregnancy will not have occurred.

There is no evidence giving specific data to inform the choice of method of termination although many clinicians prefer surgical methods because of the risk of unpredictable bleeding with medical and conservative management, and the limitation of having to admit the mother for several days.

Therapeutic cover for the procedure depends on the specific bleeding disorder but oral tranexamic acid is usually sufficient afterwards until bleeding has settled and for at least 5 days. It is appropriate to consider an ultrasound examination prior to discharge to ensure the uterus is empty with no retained products of conception. All women should be informed to report any excess bleeding and have direct contact with the haemophilia centre, with early gynaecological review.

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11. Recommendations for future research

Multicentre studies are required to determine the:

- optimal timing and use of tranexamic acid and DDAVP
- best approach to imaging for ICH in the neonate
- suitability of long-acting factor concentrates to cover delivery
- effectiveness of immunoglobulin and steroids in the treatment of fetal alloimmune thrombocytopenia related to maternal platelet disorders.

12. Auditable topics

- Percentage of women who receive prepregnancy counselling (100%).
- Blood loss and appropriateness of transfusion at delivery (90% appropriate).
- Percentage of women, with moderate or severely low baseline factor levels, who have postpartum levels measured and documented (100%).

13. Useful links and support groups

- UK Haemophilia Centre Doctors' Organisation [www.ukhcdo.org/].
- World Federation of Haemophilia [www.wfh.org/].
- Talking Red - a project of the Haemophilia Society [http://www.talkingred.org/].

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Appendix I: Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/green-top-development). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

A	At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice points

✓	Recommended best practice based on the clinical experience of the guideline development group

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Appendix II: Stratification of maternal bleeding risk

Risk level	Stratification of maternal bleeding risk	Suggested management of delivery (and note for postpartum care)
High risk	• Type 3 VWD • Severe (homozygous) rare coagulopathies • Severe platelet function disorders • Haemophilia carriers with a significant bleeding history	Adequate replacement therapy to be given after the onset of established labour. Avoid central neuraxial anaesthesia unless adequate replacement therapy has been confirmed. Maintain normal levels for at least 3 days postpartum or 5 days for caesarean section.
Medium risk	• Type 2 VWD • Mildly reduced third trimester maternal levels of factor VIII, IX or VWF activity • Factor XI deficiency with clinical bleeding phenotype	Adequate replacement therapy to be given after the onset of established labour. Avoid central neuraxial anaesthesia unless adequate replacement therapy has been confirmed. Maintain normal levels for at least 3 days postpartum or 5 days for caesarean section.
Mild risk	• Mild platelet dysfunction disorders • Carriers for haemophilia with third trimester factor VIII/IX levels $\geq$ 0.5 iu/ml • Type 1 VWD with corrected VWF activity > 0.5 iu/ml	Consider tranexamic acid for delivery and postpartum.
Unlikely to be at risk	• Rare coagulopathies without bleeding phenotype (e.g. heterozygous factor V, VII, X, XI deficiency) • Factor XII deficiency (any severity)	No replacement therapy needed. Able to have central neuraxial anaesthesia.

Note: Dysfibrinogenaemia tends to be associated with thrombosis but may cause bleeding.
Abbreviations: VWD von Willebrand disease; **VWF** von Willebrand factor.

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Appendix III: Methods for prenatal diagnosis[228–238]

Investigation/ procedure	Timing: weeks of gestation	Important information	Recommendations
Noninvasive PND for fetal sex determination	> 9	PCR analysis of cffDNA, originating from the placenta and present in maternal blood, permits noninvasive determination of fetal sex early in pregnancy. Overall sensitivity of 95% and specificity of 98% are reported.[228] cffDNA is detectable from 5 weeks of gestation[229] and is cleared from the maternal circulation within hours of childbirth, hence the analysis is pregnancy specific. UK laboratories advise testing for cffDNA after at least 9 weeks of gestation in order to achieve good sensitivity. If the fetus is female, no Y chromosome DNA can be detected; however, alternatively, this may be due to the presence of insufficient fetal DNA in the maternal sample. Inconclusive results are reported in up to 13% of cases and necessitate repeat testing.[230] Sexing by cffDNA testing is not valid in multiple pregnancies since false sexing of a fetus may occur in the case of vanishing twin conception; where a male fetus has died and a female has survived.[230] Ultrasound scanning should always be performed to exclude multiple pregnancy. The limitations of fetal sexing by cffDNA analysis must be explained to patients prior to testing. Fetal sex should be confirmed by US at 20 weeks of gestation.	***Fetal sexing by analysis of cffDNA in maternal blood should be offered to all women who are carriers of haemophilia A or B who have singleton pregnancies. This should be performed after 9 weeks or more of gestation.*** ***Fetal sex should be confirmed by US at 20 weeks of gestation.***
CVS	11^{+0}–13^{+6}	Genetic analysis is carried out for the familial mutation(s) in at-risk fetuses (e.g. only male fetuses in X-linked conditions, including haemophilia A and B).	***CVS may be offered between 11^{+0} and 13^{+6} weeks of gestation.*** ***An independent maternal blood sample should be provided to the laboratory for confirmatory mutation analysis alongside the PND sample.***
Amniocentesis for PND in early pregnancy	15+	Genetic analysis is carried out for the familial mutation(s) in at-risk fetuses (e.g. only male fetuses in X-linked conditions, including haemophilia A and B).	***Amniocentesis may be offered after 15 weeks of gestation for PND when CVS is not available or at > 34 weeks of gestation to inform clinical management plans for delivery of an at-risk fetus.***

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Appendix III. (Continued)

Investigation/ procedure	Timing: weeks of gestation	Important information	Recommendations
Amniocentesis in late pregnancy to inform clinical management of child birth	34+	Genetic analysis is carried out for the familial mutation(s) in order to inform the delivery of at-risk fetuses (e.g. only male fetuses in X-linked conditions, including haemophilia A and B).[231,232] The majority of mutations in VWD, haemophilia A and haemophilia B can usually be reliably detected in DNA extracted from AF samples, providing there are adequate numbers of fetal cells in the sample. AF in later pregnancy may contain few viable fetal cells and the resulting quality of DNA available for extraction may be poor. High-quality DNA is particularly important for successful genotyping for the *F8* intron 22 inversion mutation.	***An independent maternal blood sample should be provided to the laboratory for confirmatory mutation analysis alongside the PND sample.***
PGD	Genetic analysis performed prior to implantation of IVF-generated embryo	PGD,[233] an IVF-based process, is an option for couples at risk of transmitting a heritable disorder to their offspring: • Couples who wish to avoid having an affected child, but for religious, cultural or personal reasons would not consider termination of an affected pregnancy. • Couples with concurrent infertility since PGD requires couples to undergo IVF. Genetic analysis is performed on oocyte/zygote/embryo for: • Gender determination, allowing selective implantation of female embryos. • Specific genetic analysis for causative haemophilia mutation,[234–237] permitting the exclusion of affected male embryos for implantation. Details of centres offering PGD and practice guidelines for PGD are available at: https://www.eshre.eu/Data-collection-and-research/Consortia/PGD-Consortium/PGD-Consortium-Publications.aspx	***The options for and availability of PGD should be explained to couples as part of the genetic counselling process.***
Noninvasive PND for disease-specific diagnosis	>9	Advances in genetic testing technologies offer the possibility to carry out noninvasive disease-specific PND on cffDNA.[238] These applications, however, are not yet available in general clinical practice.	

Abbreviations: AF amniotic fluid; **cffDNA** cell-free fetal DNA; **CVS** chorionic villus sampling; **IVF** in vitro fertilisation; **PCR** polymerase chain reaction; **PGD** preimplantation genetic diagnosis; **PND** prenatal diagnosis; **US** ultrasound; **VWD** von Willebrand disease.

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Appendix IV: Risk stratification of bleeding risk for the fetus/neonate

Risk stratification of bleeding risk for the fetus/neonate		
Risk level	**Possible or confirmed fetal diagnosis**	**Suggested management of delivery**
High risk	• Males with severe and moderate haemophilia A or B • Type 3 VWD • Severe (homozygous) rare coagulopathies or severe platelet disorders	Consider third trimester amniocentesis to diagnose disease (see PND table). Discuss mode of delivery taking maternal and fetal factors into consideration, but avoid midcavity forceps, ventouse delivery, FBS, FSE, rotational forceps and external cephalic version. Cord sample for factor assay. Oral vitamin K, unless the result is known to be normal.
Medium risk	• Males with mild haemophilia A or B • Type 2 VWD	Consider third trimester amniocentesis to diagnose disease. Avoid midcavity forceps, ventouse, rotational forceps and external cephalic version. Judicious use of FBS and FSE to facilitate vaginal delivery Cord sample for factor assay. Oral vitamin K, unless the result is known to be normal.
Mild risk	• Clinically moderate or severe type 1 VWD in family • Female fetuses who are obligate/possible carriers of severe haemophilia B • Mild platelet function disorders	Consider avoidance of ventouse and external cephalic version. Judicious use of rotational forceps, FBS and FSE.
Unlikely to be at risk	• Clinically mild type 1 VWD in family • All other obligate/possible haemophilia carrier female fetuses • Heterozygous rare coagulopathies	No special precautions.

Abbreviations: FBS fetal blood sampling; **FSE** fetal scalp electrode; **PND** prenatal diagnosis; **VWD** von Willebrand disease.

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Appendix V: Neonatal bleeding risks and management

Factor	Risk of early bleeding in severe deficiency	Factor/platelet activity in normal term neonates	Diagnosis of severe and moderate deficiency	Diagnosis of mild deficiency[a]
Factor VIII	ICH incidence 1–4%	Normal or mildly increased	Yes	Possible at birth in most cases but re-test at 3–6 months to confirm levels.
Factor IX	ICH reported	Reduced	Yes	Testing required at 3–6 months of age.
VWF	ICH reported	Increased	Yes in type 3 and some type 2 deficiencies	Testing should not be undertaken unless clinically indicated until 6 months of age.
Fibrinogen	ICH and umbilical bleeding reported	Normal or slightly reduced (assay dependent)	Yes	Usually possible at birth. Confirmation required at 3–6 months of age.
Factor II	ICH and umbilical bleeding reported	Reduced	Yes	Testing required at 3–6 months of age.
Factor V	ICH reported	Normal or slightly reduced	Yes	Usually possible at birth. Confirmation required at 3–6 months of age.
Factor VII	ICH reported	Reduced	Yes	Testing required at 3–6 months of age.
Factor X	ICH and umbilical bleeding reported	Reduced	Yes	Testing required at 3–6 months of age.
Factor XI	Spontaneous bleeding seems uncommon Post-surgical bleeding reported	Reduced	Yes	Testing required at 3–6 months of age.
Factor XIII	ICH and umbilical bleeding reported	Reduced	Yes	Testing required at 3–6 months of age. Mild deficiencies may not be clinically significant.
Glanzmann's thrombasthenia	Severe bleeding appears relatively uncommon	Neonatal platelets are generally hyporeactive	Yes. PFA-100 can be used for screening. Definitive testing is PMG analysis by flow cytometry.	NA
Bernard Soulier syndrome	Severe bleeding appears uncommon	Neonatal platelets are generally hyporeactive	Yes. PFA-100 can be used for screening. Definitive testing is PMG analysis by flow cytometry.	NA

[a]Testing at birth may not be appropriate in all cases.

Abbreviations: ICH intracranial haemorrhage; **PFA** platelet function assay; **PMG** platelet membrane glycoprotein; **VWF** von Willebrand factor.

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