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Investigation and management of haemorrhagic disorders in pregnancy

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Introduction

Bleeding and blood loss associated with pregnancy and delivery remain important causes of morbidity. Although catastrophic bleeding is fairly rare nowadays, haemorrhage, particularly after giving birth, is still one of the leading causes of maternal mortality.[1]

Obstetric haemorrhage may be associated with specific complications of pregnancy or labour, or it may be due to an inherited or acquired bleeding diathesis. Obstetricians confronted with a patient who is bleeding, or who gives a personal or family history of bleeding or excessive bruising, should be alert to the possibility of an underlying inherited or acquired haemostatic defect. Each hospital should have a set of management guidelines for severe haemorrhage and must have 24 hour ready access to diagnostic laboratory facilities and advice from a designated haematologist. Although there are modern alternatives to blood, rapid access to blood and blood products is an absolute requirement for acceptable obstetric practice. Therefore, laboratory facilities for blood grouping and compatibility testing should be on site close to the maternity unit.

Haemostatic changes in normal pregnancy

Normal pregnancy is associated with major changes in the coagulation and fibrinolytic systems—the concentration of many coagulation factors increasing and plasma fibrinolytic activity decreasing as the concentrations of plasminogen activator inhibitors progressively rise. Fibrinogen increases from early pregnancy onwards to almost double its pre-pregnancy value by term. Both factor VIII (FVIII) and von Willebrand factor (vWf) rise steadily throughout pregnancy. Factors VII and X also increase very significantly during pregnancy, but the other vitamin K dependent clotting factors, factors II and IX and factor XII, show a less significant or no rise and factors XI and XIII may fall slightly.

The platelet count does not normally change significantly during pregnancy, although some authors have reported a slight drop in the count in the third trimester. The bleeding time remains normal throughout pregnancy.

Screening tests used for the investigation of bleeding—the activated partial thromboplastin time (APTT) and the prothrombin time (PT)—are within normal adult ranges during pregnancy, but in the third trimester the PT and the APTT are at the lower (shorter) limits of normal or slightly shortened, and this must be taken into account when assessing coagulation screen results from pregnant women.

Inherited bleeding disorders

In general, pregnant women with inherited bleeding disorders and the female partners of men with these defects should be managed by an obstetric unit allied with a haemophilia centre and a neonatal intensive care unit.

The most common inherited bleeding defects involve factor VIII deficiency (haemophilia A), factor IX deficiency (haemophilia B), and von Willebrand factor deficiency (von Willebrand's disease). These will be discussed at length and the more uncommon inherited bleeding disorders mentioned briefly thereafter.

Haemophilia A and haemophilia B—The prevalences of haemophilia A and haemophilia B in the United Kingdom population are 90 per 1 000 000 and 20 per 1 000 000, respectively. Most female carriers of these X linked recessive disorders do not have major bleeding problems, but in 10–20% of carriers extreme Lyonisation results in a substantial reduction of factor VIII or factor IX concentrations respectively (to < 40 units/dl) and, at the lowermost levels, a significantly increased risk of bleeding. Statistically, 50% of the male children of carrier females will have haemophilia and be at risk of serious bleeding.

Very rarely, homozygous haemophilia A or B may occur when a female is the offspring of a haemophilic father and a carrier mother. These women have the same risk of major haemorrhage as do affected males.

Von Willebrand's disease—Von Willebrand's disease (vWD) is the most common clinically important inherited abnormality of coagulation affecting women. Because of the very wide spectrum of clinical presentation, it is difficult to ascertain precisely the prevalence of all forms of vWD but it is more common than generally realised and may be as high as 1%.[2]

Broadly, vWD falls into three classes (table 1). Type 1 vWD—the commonest type (about 75% of patients)—is characterised by a reduction in all forms of vWf, with the highest molecular weight forms remaining

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Table 1 *Simplified classification of von Willebrand's disease*

Type	Bleeding time	FVIIIC	vWf antigen	vWf activity	Multimers
I	N or P	R	R	R	All present
IIA	P	N or R	N or R	R	Large and intermediate absent
IIB	P	N or R	N or R	R	Large absent
III	P	R or ND	R	ND	ND

N = normal P = prolonged R = reduced ND = not detectable.

detectable. Its inheritance can be autosomal dominant or recessive and its expression very variable. In non-pregnant patients with type I vWD the vWf concentrations (by antigen and by activity assay) are between 10–40 units/dl as is the FVIIIC. The bleeding time may be slightly to moderately prolonged but is often normal and the bleeding tendency is generally mild.

The feature common to all subvariants of type II vWD is the loss of the highest molecular weight vWf multimers. Inheritance is usually autosomal dominant. In type II vWD the vWf is functionally impaired, the bleeding time is usually prolonged, and bleeding episodes tend to be more severe and more common especially in type IIA (the commonest type II subvariant—10% of all patients with vWD) than in type 1. In subtype IIB (7% of all patients with vWD) the abnormal vWf has enhanced interaction with platelet glycoprotein (Gp) 1b: these patients often have mild to moderate thrombocytopenia. Infusion of desmopressin (1-desamino-8-D-arginine vasopressin, DDAVP) may cause a further fall in the platelet count in these patients and should therefore be avoided in type IIB vWD.

Type III vWD is clinically the most severe. The prevalence in the United Kingdom of type III vWD is about one in 1 000 000. Patients with type III vWD have no detectable or only trace amounts of vWf in their circulation. Probably many patients with type III vWD are homozygous but some may be compound heterozygotes. The condition is more prevalent in cultures where consanguinity is common. In general the parents are clinically unaffected or only mildly affected although their vWf concentrations may be at or just below the lower limits of normal. Patients with type III vWD have only 1–2 units/dl factor VIIIC and therefore have a bleeding tendency which mimics moderately severe haemophilia A with the added mucosal and subcutaneous bleeding characteristic of vWD. Parents who have had a child with type III vWD require follow up and careful counselling with respect to the management of future pregnancies and the availability of prenatal diagnosis.

Most women with vWD show an increase in their FVIII and vWf concentrations during pregnancy and most do not have excessive bleeding. When bleeding does occur, it happens more frequently after birth than during pregnancy and is usually associated with sur-

gical delivery and perineal damage. This tendency is accentuated by the rapid fall in the concentration of FVIII and vWf after delivery.[3] Some patients show variable responses of their FVIII and vWf during pregnancy[4 5] and measurement of bleeding time, FVIIIC activity, vWf antigen, and vWf activity are not always predictive of which patients will bleed.[6 7]

In general, patients with type 1 vWD have increased FVIII and vWf concentrations during pregnancy and do not bleed excessively; on the other hand, patients with type II and type III do have an increased tendency to bleed. In those with type IIA vWD the large multimers of vWf antigen do not rise in all patients during pregnancy.[8] This may explain the greater risk of haemorrhage in women with type IIA vWD than in those with type I vWD. Patients with type IIB may develop worsening thrombocytopenia during pregnancy and those with type III vWD show little or no increase in their FVIII:vWf concentrations.

PRECONCEPTION COUNSELLING
As far as possible, it is essential that families with heritable bleeding disorders understand the genetic implications of their particular disorder and that young family members come forward for investigation. Haematologists responsible for providing haemophilia services need to see these family studies and counselling as an important aspect of their remit and they may want to involve an interested obstetrician at this time. Female carriers of haemophilia A or B and women with vWD or other inherited bleeding disorders should be reviewed at intervals during their reproductive life, even if they remain asymptomatic.

Pregnancy planning should be encouraged and patients with inherited bleeding disorders and carriers or potential carriers should seek specialist medical advice from their haematologist and if possible also an obstetrician before conception. This is most evident where the affected patient is female, but couples in which the potential father has a heritable bleeding defect must also be offered prepregnancy counselling to discuss the possibility of antenatal diagnosis and other aspects of the management of the planned pregnancy. Women who may require blood product treatment but who are not immune should be immunised against hepatitis B. This should be carried out before their first pregnancy, but immunisation during pregnancy is safe although not ideal and may be necessary for women not immunised before. Because of recent reports of outbreaks of hepatitis A in some haemophiliacs, immunisation against hepatitis A is now being offered to non-immune haemophiliacs and to patients with vWD who may require blood products.

It is important that as far as possible carriers of haemophilia are identified before pregnancy so that appropriate genetic counselling can be offered and women at increased risk of bleeding can be recognised. Considerable

overlap exists between clotting factor values in normal women and in obligatory carriers of haemophilia A or B, so not all carriers are identifiable by phenotype analysis. Details of carrier identification are beyond the scope of this paper and readers are referred to published papers.[9] Genetic analysis is becoming more widely available and greatly improves the correct assignment of carrier status. Where there is any doubt about a woman's carrier status, genetic testing should be offered. The possibility of antenatal diagnosis should be discussed with carriers and facilities made available when appropriate for those who wish it.[10]

Women who first present with a history suggestive of an inherited bleeding disorder when they are already pregnant may need to be managed empirically and full investigation delayed until three to six months after delivery—although with increasing identification of genetic defects, it may be possible, in some instances, to make a diagnosis in pregnancy despite a normal phenotype. A previously undiagnosed congenital bleeding disorder should be considered in a patient who is otherwise well but bleeds and bruises excessively either spontaneously, or following venepuncture, or at delivery.

MANAGEMENT OF PREGNANCY
Women with vWD and carriers of haemophilia A or B require regular review (at least every eight to 12 weeks) at a haemophilia centre throughout pregnancy for monitoring, including coagulation factor activity and, if appropriate, the concentrations of vWf antigen, vWf activity, platelet count and bleeding time (table 2). Monitoring during the third trimester (around 34–36 weeks) is particularly important as it permits final planning and discussion of the management of the forthcoming delivery.

The uptake of prenatal diagnosis in most centres is surprisingly low, with between 20% and 30% of known carriers opting for chorionic villous sampling (CVS). Modern ultrasound scanning equipment permits visualisation of fetal external genitalia and offers non-invasive techniques for identifying most male fetuses by 18 to 20 weeks. Information about the sex of the fetus is invaluable in managing pregnancy and delivery in carriers of haemophilia A or B where prenatal diagnosis has not been performed. It should be

noted that although the diagnosis of a male fetus is almost always correct, the diagnosis of a female fetus is less accurate.

Invasive procedures during pregnancy
The potential benefits and risks of invasive procedures during pregnancy, which may result in accidental maternal, fetal, or placental bleeding, must be carefully considered on an individual patient basis. Rational decisions about these procedures require input from experts experienced in the management of pregnant women with bleeding disorders. Because of the risk of haemorrhage even CVS for prenatal diagnosis may be hazardous and should be performed only after careful consideration and full discussion of the risks and benefits with the parents.

Maternal coagulation factor activity and vWf concentrations do not rise significantly until the second trimester. CVS and other invasive procedures, such as pregnancy termination, spontaneous abortion, or general surgery during the first trimester, may therefore be complicated by serious maternal haemorrhage unless coagulation factor activity is raised to 50 units/dl.

MANAGEMENT OF DELIVERY
If there is any concern over coagulation factor activity in the mother a planned delivery date is advised. On admission, a maternal blood sample should be sent for a full blood count and platelet count, coagulation screen, and appropriate coagulation factor or vWf assays, and for blood grouping and antibody screening with a request to the blood bank to retain serum for compatibility testing if that should become necessary (table 2).

In the absence of any obstetric contraindication vaginal delivery is usual but caesarean section should be considered if labour fails to progress steadily. An early recourse to caesarean section is recommended for carriers of haemophilia A or B with a known male fetus if any problem develops and the chance of an easy vaginal delivery is less likely. Operative or instrumental delivery (if necessary) should be performed by the most experienced member of staff available. Ventouse extraction should be avoided in cases where the fetus is thought to be affected. Scalp electrodes or scalp vein blood sampling can cause massive haematomata and should be avoided if possible if the fetus might have vWD, and in haemophilia A or B carriers when the fetus is known to be male or its sex is unknown. Every effort must be made to minimise maternal genital tract or perineal trauma as this greatly increases the risk of postpartum bleeding. After a difficult delivery, particularly if instruments have been required, the neonate may need blood product replacement and this should be readily available.

Blood product therapy
Factor VIII concentrations usually rise during pregnancy and in general also in haemophilia A carriers. In type I vWD, providing the FVIIIC activity exceeds 40 units/dl, no blood

Table 2 Obstetric management of women with inherited bleeding disorders: general principles

Prepregnancy diagnosis, counselling, hepatitis B immunisation	
Regular clinical and haemostasis monitoring during pregnancy	
Ultrasound "sexing" of fetus	
Avoid unnecessary invasive procedures	
On admission for delivery	Full blood and platelet counts
	coagulation investigations
	blood group and retain serum
Minimise maternal and fetal trauma at delivery	
Access to blood product replacement may be necessary	
Avoid intramuscular injections	
Collect cord blood sample for investigation	
Give neonate vitamin K$_1$ orally	
Immunisations to infant by intradermal route	
Consider hepatitis B immunisation for infant	

product replacement is required to cover uncomplicated vaginal delivery. Coagulation factor activity should be rechecked between 34–36 weeks gestation in case emergency admission or caesarean section is required. If caesarean section is planned or becomes necessary FVIIIC activity should be in excess of 50 units/dl and infusion of FVIII concentrate may occasionally be necessary to raise a type I vWD or a haemophilia A carrier's concentration of FVIIIC.

Normally factor IX activity does not rise as much as FVIII during pregnancy and female carriers of haemophilia B with low factor IX activity more frequently require specific replacement treatment to raise their factor IX activity to safe levels for vaginal delivery (40 units/dl) or caesarean section (50 units/dl). High purity factor IX concentrate should be used as factor IX concentrates containing factors II, VII, and X are potentially thrombogenic.

In carriers of haemophilia A or B, following delivery, FVIIIC and factor IX concentrations should be maintained above 40 units/dl for at least 3–4 days or for 4–5 days if caesarean section has been performed. In the presence of bleeding or wound infection a longer period of treatment may be necessary.

Frequently patients with type III and type IIA vWD and occasionally type IIB vWD require blood product treatment to raise their FVIII and vWf complex concentrations to cover delivery—even if vaginal delivery is anticipated (table 3). Prophylactic infusion of factor concentrates should start at the onset of labour aiming to raise FVIIIC and vWf activity to above 40 units/dl. FVIII concentrates which contain large amounts of the larger vWf multimers should be used—for example, 8Y; Blood Products Laboratory, or Haemate P; Hoechst.[11] Caesarean section is major surgery and vWD patients with reduced FVIII and vWf concentrations must be given appropriate FVIII and vWf replacement (as above) to raise their FVIIIC and vWf activity to above 50 units/dl before surgery. Factor VIIIC activities are used to monitor the response to infusion in patients with type I vWD and vWf activity in type II patients. Concentrations must be maintained at above 40 units/dl for 3–4 days after vaginal delivery and for 4–5 days after caesarean section.

Carriers of haemophilia A and a proportion of patients with type 1 or type II A vWD may respond to an infusion of desmopressin (DDAVP) with a rise in their FVIII and vWf

complex activities. Some haematologists and obstetricians recommend, however, that desmopressin is avoided during pregnancy and intrapartum because of its effect on oxytocin. Demospressin infusion may be used after delivery or following abortion or termination when a moderate rise in FVIII activity is required for a few days only. Desmopressin infusions after surgery may cause water retention and hyponatraemia,[12] so blood urea and electrolytes should be monitored and excessive fluid input (such as dextrose infusions) avoided. Patients with type IIB vWD should not be given desmopressin, because of the risk of causing platelet aggregation and thrombocytopenia due to binding of abnormal intermediate sized multimers of vWf antigen to platelets and subsequent platelet aggregation.[13]

Analgesia

Intramuscular analgesia should be avoided and intravenous or subcutaneous analgesia used if necessary. Providing the coagulation screen is normal, the Simplate bleeding time less than 10 minutes, and the platelet count greater than $100 \times 10^9/l$, there should be no contraindication to inserting an epidural catheter.[14] Care must be exercised before removing the catheter and in these patients with an inherited bleeding tendency it is suggested that a further coagulation screen and platelet count is performed before withdrawal of the epidural catheter. In cases of elective surgery spinal anaesthesia may be the safer option.

LESS COMMON INHERITED BLEEDING DEFECTS
Fibrinogen abnormalities

Women with hereditary hypofibrinogenaemia may sustain recurrent pregnancy loss or excessive bleeding, but successful pregnancy outcome has been described with regular replacement treatment throughout pregnancy.[15]

Other coagulation factor deficiencies

There is very limited recorded experience of pregnancy management in women with other coagulation factor deficiencies.[16] As far as possible women with these defects should be identified and counselled before pregnancy and should be managed in obstetric units allied to a haemophilia centre.

Congenital platelet disorders

Congenital platelet function disorders are uncommon, although not rare, and are usually associated with a mild bleeding diathesis. Families with disorders such as familial thrombocytopenia, Glanzmann's thrombasthenia, Bernard-Soulier syndrome, storage pool defects and disorders of platelet secretion should attend a haemophila centre and be offered counselling and care similar to that offered to families with inherited coagulopathies.

Pregnancy and delivery are documented in only a few patients with severe platelet function disorders,[17 18] but in general management

Table 3 Management of delivery and puerperium in vWD

vWD type	Delivery	Postpartum
I	Occasionally require blood product replacement Regard caesarean section as major surgery	Treat bleeds with blood products or desmopressin
IIA IIB	May require blood products Regard caesarean section as major surgery	Treat bleeds with blood products Do not use desmopressin in type IIB
III	Treat as major surgery and offer blood products	Prophylactic blood products for 3–5 days

involves the strict avoidance of unnecessary platelet transfusions, the search for platelet antibodies in patients who have previously received donor platelets, and in some patients the use of single donor platelets or platelet type specific donor platelets. In patients with storage pool defects and a history of bleeding, DDAVP may be helpful at the time of delivery.

POST PARTUM FOLLOW UP

A cord sample should be collected for investigation. Because some haemostatic factors are physiologically relatively reduced in neonates, it may be difficult to exclude a mild to moderate inherited defect at birth (in haemophilia B, vWD, or factor XI deficiency). In these children repeat investigation at three to six months is necessary.

Intramuscular injections must be avoided in children of either sex with confirmed or possible vWD and in male children of carriers of haemophilia A or B (unless they have been proved to be unaffected). In these neonates, therefore, prophylactic vitamin K_1 must be given orally and their general practitioner informed and asked to ensure that routine immunisations are given carefully intradermally or subcutaneously. Immunisation against hepatitis B should be offered. Arrangements to review mother and baby at the haemophilia centre must be made before they are discharged from the maternity unit.

Acquired bleeding disorders

Acquired bleeding disorders developing during pregnancy, at delivery, or following delivery, present a different set of problems from those faced in women with an inherited bleeding tendency. Women with inherited bleeding problems are most frequently known and otherwise well. With careful counselling, planning, and if necessary prophylaxis, they generally progress through pregnancy and delivery in a reasonably predictable way. Women who develop an acquired bleeding disorder during pregnancy or delivery do so acutely, are usually unwell, and sometimes very ill. Their bleeding disorder further complicates their progress and management and may in some instances dominate their clinical presentation.

Thrombocytopenia

The causes of thrombocytopenia in pregnancy are so numerous and varied that these will be the subject of a separate guidelines document (in preparation).

Disseminated intravascular coagulation (DIC)

Disseminated intravascular coagulation (DIC) is associated with a wide variety of clinical situations which complicate pregnancy. DIC is never a primary event but is always a secondary phenomenon triggered by the release of procoagulant material into the circulation or by damage to the vascular endothelium. Depending on the triggering event, the manifestations of DIC range from a chronic, compensated state to acute life threatening haemorrhage. The chronic DIC which occurs in pre-eclampsia or with hydatidiform mole is associated with laboratory evidence of increased platelet turnover and mildly reduced fibrinogen concentrations but usually with no excessive bleeding. Many obstetric complications—for example, placental abruption, amniotic fluid embolism, septic abortion—are however associated with a more acute release of tissue thromboplastin into the circulation with the resultant pronounced depletion of coagulation factors, increased fibrinolytic activity, and consumption of platelets and subsequent clinical bleeding.

MANAGEMENT OF ACUTE LIFE THREATENING
HAEMORRHAGE IN OBSTETRIC PATIENTS

The immediate management of haemorrhage in obstetric patients is essentially the same whether or not the bleeding is caused or exacerbated by DIC. There should be a routine planned procedure agreed by obstetricians, midwives, anaesthetists and haematologists to deal with acute haemorrhage whenever it arises. Agreed protocols should be produced and given to all staff concerned and be available in the labour ward. Early and continuing reliable communication with laboratory staff is mandatory, although the urgency of the clinical situation often demands intervention before full test results are available.

Acute obstetric bleeding is usually obvious as blood escapes from the genital tract. It may, however, be very difficult to estimate the volume of blood loss from the circulation as much of the loss may be concealed behind the placenta and in the myometrium, within the uterine cavity or the broad ligament, and total blood loss is often dangerously underestimated. In some cases of abruption, there is no visible vaginal bleeding with all the haemorrhage concealed. The rate of blood loss is probably more important than volume of blood loss, at least initially.

Source of blood loss

Obstetric bleeding occurs most commonly from the placental bed. Before birth this may be the result of a placenta implanted in the lower uterine segment (placenta praevia) or the result of abruption of a normally sited placenta. After delivery poor myometrial contraction due to hypotonia, or to retained products of conception (placenta or membranes), or blood clot may permit continuing blood loss from the placental site. Intrapartum and postpartum bleeding may also be the result of trauma—rupture of the uterine wall, tearing of the cervix or vagina, or damage to the perineum or vulval varicosities.

It is imperative that the source of bleeding is identified and dealt with as soon as possible. Shock may trigger DIC which will further complicate the bleeding tendency. Active steps to restore blood volume and oxygen carrying capacity must be instituted as a matter of urgency (table 4).

Table 4   Management of acute obstetric haemorrhage

Secure venous access and insert central venous pressure monitor
Summon additional help
Collect blood samples for cross matching and coagulation screen
Contact haematologist and blood bank
Maintain blood volume—with unmatched blood if necessary (same ABO and RhD group as patient)
Seek and deal with source of bleeding
Blood product replacement treatment if necessary

Laboratory investigation

A sample of venous blood should be sent for full blood count, coagulation screening, and cross matching. Emergency packs with all necessary samples tubes and forms should be kept available in a labour ward refrigerator. Results of coagulation screening tests must always be interpreted, bearing in mind that normally in the third trimester the APTT and PT are at the lower limits of normal. Measurement of products of plasmin digestion of fibrinogen or fibrin provides an indirect test for fibrinolysis along with a platelet count and a fibrinogen assay (Clauss method) or thrombin time will quickly distinguish coagulation screen abnormalities caused by DIC from those attributable to other causes.

Maintenance of blood volume

Severe bleeding is an obstetric emergency. The aim of management should be to maintain the circulation and stop the bleeding. Help from the most senior obstetricians, anaesthetists, and midwives available should be sought. The laboratory should be notified immediately of the problem. Venous access should be achieved at two sites using large bore cannulae. Blood pressure and pulse should be monitored and a central venous line should be inserted.

Blood is the best fluid to replace blood loss. Wherever possible this should have been shown to be compatible with the patient's blood before issue, but in an emergency it may be necessary to issue unmatched blood. Pregnant women who have been attending for antenatal care will have their blood group and antibody status already known. Providing this blood group has been confirmed, unmatched blood of the patient's own ABO and RhD group is preferable to unmatched group O RhD negative blood. Immediately on receipt in the laboratory the patient's blood sample should be ABO and RhD grouped by rapid techniques and ABO incompatibility with issued units excluded by a rapid spin crossmatch (a spin agglutination test after 2–5 minutes' incubation at room temperature). It should usually be possible to recheck the patient's blood group and exclude major incompatibility before a large amount of blood is transfused. Unmatched group O RhD negative, Kell negative, Duffy negative blood should only be issued in the very rare event of life threatening haemorrhage in a woman whose blood group is unknown.

Whilst awaiting blood, the blood volume must be expanded with crystalloids such as Hartmann's solution (up to 2 litres). However, these leave the circulation rapidly and must be considered as a "first-aid" measure only. If available, a 4·5% solution of human albumin may be used, otherwise other colloids such as Haemaccel (Hoechst) or Gelofusine (Vifor)—up to 1·5 litres—are preferable to dextrans which interfere with compatibility testing and with platelet function. Two lines are usually necessary to allow blood and other products to be infused simultaneously. After the initial transfusion fluid replacement should be monitored with central venous pressure monitoring.

Stopping the bleeding

Although the circulation can be maintained in the short term, survival of the patient is dependent on stopping the bleeding. How this is done depends on whether the bleeding occurs before or after birth.

ANTEPARTUM HAEMORRHAGE

If the bleeding is severe delivery and the emptying of the uterus is the only way to stop it. If blood loss is not adequately replaced acute renal tubular necrosis may occur.

Placenta praevia

In the case of placenta praevia, most of the bleeding will be apparent. Coagulation defects are rare and the main problem is blood replacement. Delivery must be by caesarean section. If the placenta is anterior, further severe haemorrhage may occur during delivery. After the placenta is delivered the lower uterine segment does not contract as well as the upper segment and bleeding can continue. If bleeding is not controlled at delivery the management is similar to that required for postpartum haemorrhage.

Placental abruption

With placental abruption, the blood loss is always underestimated and replacement should take account of this. As bleeding may largely be retroplacental and several litres of blood may be concealed behind the placenta, the amount of blood issuing from the vagina before delivery is no indicator of the extent of placental detachment or of the subsequent blood loss. There is usually a concomitant coagulation defect and it is the most common cause of acute pregnancy related DIC. The degree of haemostatic disturbance is related to the degree of placental separation.

The mere suspicion that a patient may have placental abruption should prompt an urgent coagulation screen, full blood and platelet counts, and a blood sample for immediate blood group and antibody screen with compatibility testing, if and when appropriate.

In placental abruption, prevention or correction of hypovolaemia is the primary concern with expeditious vaginal delivery whenever possible. The bleeding and coagulation defects will not be controlled until after delivery. There should be prompt replacement of blood volume to maintain renal perfusion. Although depleted coagulation factors should be replaced, the consumption will

continue until the uterus is emptied. Fresh frozen plasma (1 litre) is often sufficient to correct the coagulation defect, but severe depletion of fibrinogen (to less than 0·8 g/l) requires the infusion of 10–15 units of cryoprecipitate. Thrombocytopenia (platelet count of less than 50×10^9/l) may require correction by transfusion of platelet concentrates. Further coagulation investigation and platelet counts are required to monitor response to replacement treatment and the ongoing clinical condition to judge the requirement for further replacement.

Having initiated management of hypovolaemia and taken samples for coagulation screening and for blood group, measures to expedite delivery must be addressed. Vaginal examination should be carried out to assess the state of the cervix. In parous women, amniotomy may be enough to stimulate labour and lead to prompt delivery, but others may, in addition, require oxytocin infusion. If the mother is relatively stable, the fetus can tolerate the delay and, providing damage to the birth canal and perineum can be avoided, vaginal delivery is preferable. If there is any sign of fetal distress or if vaginal delivery is not imminent or seems likely to be difficult caesarean section may be necessary. In this case, blood volume and coagulation factor replacement before surgery is essential as far as it is possible. Delivery should not be delayed to achieve this, however, as emptying the uterus will stop the consumption and help in the correction of the factor deficiency. Fresh frozen plasma and platelet infusion can be given as the operation is started. If the fetus is already dead, caesarean section is seldom indicated except where, despite adequate oxytocin stimulation, cervical dilation does not occur.

Once the fetus and placenta are delivered, myometrial retraction will usually dramatically reduce or stop placental site bleeding, but measures to stimulate myometrial function may be essential and care must be taken to ensure that the uterus remains well contracted. Abdominal or perineal wound healing may be difficult or slow.

Epidural analgesia is potentially hazardous in patients with DIC and should be avoided. Although heparin has been used in DIC,[19] in general its use is not recommended in DIC associated with pregnancy where the circulation is not intact because of the placental bed.

POST PARTUM BLEEDING
Excessive bleeding after delivery can result from one of the above pre-existing antenatal problems or be caused by retained products of conception or trauma to the genital tract. Immediate intravenous access should be obtained as outlined above and blood drawn for a full blood count, platelet count, a coagulation screen and cross matching. The blood loss should be replaced and coagulation defects, where identified, should be corrected with appropriate blood product replacement treatment as outlined above.

The placenta and membranes should be re-examined to check for any evidence of retained products. The fundus should be examined to make sure that the uterus is contracted. If the uterus is atonic, an intravenous injection of 10 units of oxytocin or 0·5 mg of ergometrine should be given. After this an infusion of oxytocin should be started to keep the uterus contracted. If the haemorrhage continues, Hemabate (Upjohn), a prostaglandin F analogue, should be given either intramuscularly or, in extreme circumstances, directly into the myometrium. These actions should be accompanied by bimanual compression of the uterus.

If there is continual bleeding from the genital tract, the patient should be examined under the appropriate anaesthesia. If the bleeding is coming through the cervix, the cavity should be explored and any retained products removed followed by the use of oxytocics. If the bleeding is coming from lower in the genital tract, the cervix and vagina should be examined for tears and promptly repaired.

If there are persistent problems senior help should be summoned promptly. If bleeding continues from the uterus laparotomy should be carried out to exclude the possibility of uterine rupture. If there is persistent bleeding from the placental site oversewing of the bleeding points should be considered. Early recourse to hysterectomy may be life saving, with tying of the internal iliac arteries a further option. Although the urinary tract is at risk in this situation, most damage can be repaired at a later date and haemostasis is the primary aim. In the acute situation aortic compression, either at laparotomy or by abdominal compression, may control bleeding, enough to visualise the bleeding points or for senior support to arrive.

In the presence of persisting severe haemorrhage, coagulation factors may need to be replaced rapidly. A litre of fresh frozen plasma and 10 units of cryoprecipitate may be thawed and issued empirically before coagulation screening tests are completed. Fresh frozen plasma contains all of the coagulation factors normally present in plasma. Cryoprecipitate has the advantage of a higher concentration of fibrinogen per volume. If the platelet count has fallen below 50×10^9/l platelet concentrates may be suggested, but often haemostasis and control of bleeding can be achieved without platelet transfusion.

The risks and disadvantages of fibrinolytic inhibitors (tranexamic acid, aprotinin) outweigh their potential benefits in most obstetric haemorrhages. In a very few cases where persisting postpartum bleeding can clearly be shown to be associated with excessive fibrinolytic activity (a shortened euglobulin clot lysis time) and no trauma, antifibrinolytic agents may be tried with caution.

Management of less severe obstetric bleeding
In patients who are bleeding less severely management can be tailored on an individual basis but the broad principles remain the

same as for life threatening haemorrhage. Extra help, including laboratory staff and anaesthetic staff, must be alerted early on; blood samples for full blood count, coagulation screening, and compatibility testing should be dispatched urgently; and infusion lines should be in place and a careful search to identify and deal with the source of bleeding made. If transfusion is necessary crossmatched blood is always preferable to unmatched blood.

If time permits the results of the coagulation screening tests may provide a scientific basis on which to prescribe blood product replacement. In practice, though, this will usually be fresh frozen plasma in patients without evidence of severe fibrinogen depletion or a combination of fresh frozen plasma and cryoprecipitate in patients with fibrinogen concentrations of less than 0·8 g/l.

OTHER CAUSES OF ACQUIRED OBSTETRIC BLEEDING

Aminotic fluid embolism

Amniotic fluid embolism is an uncommon generally fatal complication of pregnancy. It may occur during or shortly after labour or at caesarean section. If the patient survives the initial event, rapid and virtually total consumption of clotting factors and platelets ensues, leading to catastrophic exsanguinating uterine haemorrhage. Typically the patient is in or has just completed a strenuous labour with an intact amniotic sac when she suddenly collapses profoundly shocked, cyanosed with respiratory distress, and bleeding from venepuncture sites and from the genital tract.

Cardiopulmonary resuscitation may be necessary and preparation made for immediate delivery if this has not occurred. Blood products, including fresh frozen plasma, cryoprecipitate, and platelets are urgently required and must be used empirically. If occurring after delivery 10 000 units of heparin given intravenously may help to arrest this cycle of coagulation and haemolysis.

Retained dead fetus

This is now a rare occurrence. To cause detectable consumption of coagulation factors, the fetus has to be retained in utero for three to four weeks after its demise. Spontaneous labour usually supervenes within two weeks of fetal death and current obstetric practice would be to induce labour if it did not occur spontaneously shortly after fetal death. Although significant consumptive coagulopathy is a rare complication of a retained dead fetus, it is recommended that a coagulation screen and platelet count are performed on all mothers with a dead fetus in utero before inducing labour, or as early as possible in a spontaneous labour. Replacement therapy is rarely necessary. If a coagulation defect is found the presence of antiphospholipid antibodies should be sought as they could have contributed to fetal death. In the unusual circumstances of a dead twin or selective fetocide where the dead fetus may remain in utero for a number of weeks, a coagulation defect may occur. In this situation low dose heparin may be of benefit but it is not without risk to the mother and her surviving fetus. These pregnancies require close management and advice from centres with previous experience.

Acquired inhibitors of coagulation

Rarely, a bleeding tendency similar to that observed in haemophilia A may occur secondary to the development of an inhibitor to factor VIII. Most cases present two to three months after delivery but the inhibitor may develop during pregnancy[20] or cause severe bleeding in the early puerperium.[21] The inhibitor is usually an IgG antibody. It may disappear spontaneously or after immunosuppressive treatment with steroids. In at least 50% of women the inhibitor will be undetectable a year after initial detection[22] and it rarely recurs with subsequent pregnancies.[23] Frequent monitoring of the inhibitor activity is essential to aid planning of treatment if bleeding should occur. A trial of prednisolone or intravenous immunoglobulin may be considered.

Management of bleeding in these patients is very difficult, involving the use of human or porcine factor VIII, or activated prothrombin complex concentrates. It is very much the province of haematologists with experience in managing patients with pathological coagulation inhibitors.

Acute hepatic failure

Acute fatty liver of pregnancy is acute liver failure occurring during pregnancy unrelated to infection, hepatotoxic drugs, or chemicals or haemolytic uraemic syndrome.[24] It can also occur in association with pre-eclampsia. Characteristically the patient rapidly develops clinical and biochemical evidence of liver failure in association with a severe coagulopathy, reduced platelet count, raised concentrations of fibrin and fibrinogen degradation products (FDPs), reduced fibrinogen, and extremely low antithrombin (AT). The biochemical findings are those of liver function impairment with low plasma albumin and vitamin K dependent coagulation factors. The liver enzymes are often not substantially increased.

It is important to realise the seriousness of this situation. The perinatal mortality is approaching 50% with the maternal mortality at 30%. If delivery is not expedited the fetus will die in utero followed by the death of the mother. After delivery the mother will hopefully recover with supportive management. Some benefits from correction of the coagulopathy after administration of AT have been suggested.[25] Infusion of material containing AT may be worth considering in this dire clinical condition.

The advice contained in these guidelines is believed to represent the state of the art at the time of going to press. It is policy to revise the guidelines as new developments occur, but it may not be possible to do this at the time of such changes and the guidelines should always be used with due regard to current acceptable practice.

Comments are invited to assist the review process. All correspondence regarding the guidelines should be addressed to: BCSH Secretary, British Society for Haematology, 2 Carlton House Terrace, London SW1Y 5AF

1 Department of Health, Welsh Office, Scottish Home and Health Department, Department of Health and Social Services, Northern Ireland. *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–1987*. London: HMSO, 1991.

2 Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood* 1987;69:454–9.

3 Krishnamurthy M, Miotti AB. von Willebrand's disease and pregnancy. *Obstet Gynecol* 1977;49:244–7.

4 Hill FGH, George J, Enayat MS. Changes in VIII:C, VIIIR:AG, WF and ristocetin-induced platelet aggregation during pregnancy in women with von Willebrand's disease. *Br J Haematol* 1982;50:691.

5 Adashi EY. Lack of improvement in von Willebrand's disease during pregnancy. *N Engl J Med* 1980;303:1178.

6 Lipton RA, Ayromlooi J, Coller BS. Severe von Willebrand's disease during labor and delivery. *JAMA* 1982;248:1355–7.

7 Greer IA, Lowe GDO, Walker JJ, Forbes CD. Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. *Br J Obstet Gynaecol* 1991;98:909–18.

8 Takahashi N. Studies on the pathophysiology and treatment of von Willebrand's disease VI. Variant von Willebrand's disease complicating placenta previa. *Thromb Res* 1983;31:285–96.

9 Peake IR, Lillicrap DP, Boulyjenkov V, *et al*. Report on Joint WHO/WFH Meeting on the control of haemophilia: carrier detection and prenatal diagnosis. *Blood Coagulation and Fibrinolysis* 1993;4:313–44.

10 Old JM, Ludlam CA. Antenatal diagnosis in paediatric haematology. In: Hann IM, Gibson BES, eds. *Clinical haematology: International practice and research 4·2*. London: Baillière Tindall, 1991:429–58.

11 UK Haemophilia Centre Directors Committee. Recommendations on the choice of therapeutic products for the treatment of patients with haemophilia A, haemophilia B and von Willebrand's disease. *Blood Coagul Fibrinolysis* 1992;3:205–14.

12 Lowe GDO, Pettigrew A, Middleton S, Forbes CD, Prentice CRM. DDAVP in haemophilia. *Lancet* 1977; ii:614–5.

13 Rick ME, Williams SB, McKeown LP. Thrombocytopenia associated with pregnancy in a patient with type 11B von Willebrand's disease. *Blood* 1987;11: 786–9.

14 Letsky EA. Haemostasis and epidural anaesthesia. *Int J Obstet Anaesth* 1991;1:51–4.

15 Grech H, Majumdar G, Lawrie AS, Savidge GF. Pregnancy in congenital afibrinogenaemia: report of a successful case and review of the literature. *Br J Haematol* 1991;78:571–2.

16 Bern MM. Acquired and congenital coagulation defects encountered during pregnancy and in the fetus. In: *Haematologic disorders in maternal fetal medicine*. Bern MM, Frigoletto FD, eds. New York: Wiley-Liss, 1990:395–448.

17 Michalas S, Malamitsi-Puchner A, Tsevrenis H. Pregnancy and delivery in Bernard-Soulier syndrome. *Acta Obstet Gynecol Scand* 1984;63:185–6.

18 Sundqvist SB, Nilsson IM, Svanberg L, Cronberg S. Pregnancy and parturition in a patient with severe Glanzmann's thrombasthenia. *Scand J Haematol* 1981; 27:159–64.

19 Thiagarajah S, Wheby MS, Jain R, May H V, Bourgeois J, Kitchin JD. Disseminated intravascular coagulation in pregnancy: The role of heparin therapy. *J Reprod Med* 1981;26:17–20.

20 Voke J, Letsky E. Pregnancy and antibody to factor VIII. *J Clin Pathol* 1977;30:928–32.

21 Reece EA, Romero R, Hobbins J. Coagulopathy associated with factor VIII inhibitor. A literature review. *J Reprod Med* 1984;29:53–8.

22 Green D, Lechner K. A survey on 215 non-hemophilic patients with inhibitors to factor VIII. *Thromb Haemostas* 1981;45:200–3.

23 Vincente V, Alberca I, Gonzales R, Alegre A. Normal pregnancy in a patient with a postpartum factor VIII inhibitor. *Am J Hematol* 1987;24:107–9.

24 Kaplan MM. Acute fatty liver of pregnancy. *N Engl J Med* 1985;313:367–70.

25 Liebman HA, McGehee WG, Patch MJ, Feinstein DI. Severe depression of antithrombin III associated with disseminated intravascular coagulation in women with fatty liver of pregnancy. *Ann Intern Med* 1983;98:330–3.