

Acquired and Congenital Hemostatic Disorders in Pregnancy and the Puerperium

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During normal pregnancy, a series of progressive changes in hemostasis occur that are overall pro-coagulant and help prevent excessive bleeding at the time of delivery. The concentrations of coagulation factors VII, VIII, X and von Willebrand factor (vWF) rise significantly (Table 1) and are accompanied by a pronounced increase in fibrinogen levels (up to two-fold from non-pregnant levels). Factor V and factor IX levels remain unchanged or increase only slightly. Factor XIII levels tend to decrease in late pregnancy after an initial increase in early pregnancy. Markers of coagulation activation such as prothrombin fragments (PF1+2), thrombin-antithrombin complexes (TAT) and D-dimer are increased, while a decrease in physiological anticoagulants is manifested by a significant reduction in protein S activity and acquired activated protein C (APC) resistance. Fibrinolysis is inhibited not only by the rise in endothelium-derived plasminogen activator inhibitor-1 (PAI-1), but also by placenta-derived PAI-2. Microparticles derived from maternal endothelial cells and platelets, and from placental trophoblasts, may contribute to the pro-coagulant effect¹. Although concentrations of soluble tissue factor (TF) remain constant during normal pregnancy², monocyte TF activity and expression are lower when compared with those in non-pregnant women, possibly acting to counterbalance the pro-coagulant changes^{3,4}. Local hemostasis at the placental

trophoblast level is characterized by increased TF expression and low expression of tissue factor pathway inhibitor (TFPI)¹. Approximately 4 weeks post-delivery, the hemostatic system returns to that of the non-pregnant state⁵.

Although the overall balance shifts towards hyper-coagulability, occasionally medical conditions coincident with pregnancy and complications of pregnancy itself put excessive demands on maternal physiology and may result in a bleeding tendency. This chapter describes acquired and congenital hemostatic disorders that may lead to hemorrhagic complications in the obstetric patient. Though many of these conditions are rare and the average health care provider may see few if any during a long career, their recitation here is appropriate as some are associated with a tendency for the parturient to have postpartum hemorrhage (PPH).

ACQUIRED DISORDERS OF HEMOSTASIS

Thrombocytopenia

Thrombocytopenia is the most common hemostatic abnormality and may complicate up to 10% of all pregnancies. The normal platelet count ranges from $150\text{--}400 \times 10^9/\text{l}$, and thrombocytopenia is defined as a count of less than $150 \times 10^9/\text{l}$. The platelet count may decline by approximately 10% during normal pregnancy⁶. Spontaneous bleeding is unusual unless the count has fallen to below $30 \times 10^9/\text{l}$, but surgical bleeding or PPH may occur as a consequence of a platelet count of less than $50 \times 10^9/\text{l}$. Thrombocytopenia in pregnancy may result from a variety of causes (Table 2). The timing of onset of these disorders during pregnancy and their clinical manifestations often overlap, making the identification of individual causes of thrombocytopenia sometimes problematic.

It is important to consider spurious thrombocytopenia as a possible cause of decreased platelet count before embarking on extensive investigations or treatment. This is a laboratory artifact due to platelet aggregation *in vitro* caused by EDTA-induced antibodies against platelet GPIIb/IIIa receptors⁷ and can be diagnosed by visual inspection of the blood film, when platelet changes are readily visible.

Table 1 Coagulation system changes in normal pregnancy

	Increased	Decreased	No change
<i>Systemic changes</i>			
Procoagulant factors	I, V, VII, VIII, IX, X	XIII	V, IX, PC, AT
Anticoagulant factors	Soluble TM	PS	
Adhesive proteins	vWF		
Fibrinolytic proteins	PAI-1, PAI-2	t-PA	Soluble TF
Tissue factor (TF)		Monocyte TF	
Microparticles (MP)	MP		
<i>Local placental changes</i>	TF	TFPI	

TM, thrombomodulin; PS, protein S; PC, protein C; AT, antithrombin; vWF, von Willebrand factor; PAI, plasminogen activator inhibitor; t-PA, tissue plasminogen activator; TFPI, tissue factor pathway inhibitor.

Modified from Brenner B. Haemostatic changes in pregnancy. *Thromb Res* 2004;114:409-14

Table 2 Causes of pregnancy-associated thrombocytopenia

<i>Pregnancy-specific</i>	<i>Not pregnancy-specific</i>
Gestational (incidental) thrombocytopenia	Idiopathic thrombocytopenic purpura (ITP)
Pre-eclampsia	Thrombotic thrombocytopenic purpura (TTP)
HELLP syndrome	Hemolytic uremic syndrome (HUS)
(hemolysis, elevated liver enzymes and low platelets)	Systemic lupus erythematosus
Acute fatty liver of pregnancy (AFLP)	Viral infection (HIV, CMV, EBV)
	Antiphospholipid antibodies
	Consumptive coagulopathy
	Drug-induced thrombocytopenia
	Type 2B von Willebrand disease
	Congenital

CMV, cytomegalovirus; EBV, Epstein-Barr virus

From McCrae KR. Thrombocytopenia in pregnancy: differential diagnosis, pathogenesis and management. *Blood Rev* 2003;17:7-14

Gestational thrombocytopenia

Gestational, or incidental, thrombocytopenia (GT) is the most common cause of thrombocytopenia in pregnancy, affecting 5% of all pregnant women and accounting for more than 75% of cases of pregnancy-associated thrombocytopenia. It presents as a mild to moderate thrombocytopenia ($100-150 \times 10^9/l$), which is detected incidentally often for the first time during the third trimester of pregnancy. The platelet count returns to normal within 7 days of delivery. GT is the physiologic thrombocytopenia that accompanies normal pregnancy and is thought to be due to hemodilution and/or accelerated platelet clearance^{8,9}. It is an entirely benign condition and is not associated with maternal hemorrhage or fetal or neonatal thrombocytopenia. It is, however, necessary to monitor the platelet count during pregnancy and, if it falls below $100 \times 10^9/l$, the diagnosis must be reviewed. Rare cases, subsequently confirmed as GT, have had counts as low as $50 \times 10^9/l$ ¹⁰. Epidural anesthesia is considered safe if the maternal platelet count is greater than $80 \times 10^9/l$. Delivery should proceed according to obstetric indications. Traumatic delivery, use of fetal scalp electrodes and fetal scalp blood sampling should be avoided. If it is difficult to distinguish between GT and idiopathic thrombocytopenic purpura (ITP), a cord platelet count should be obtained.

Idiopathic thrombocytopenic purpura

ITP accounts for one to five cases of thrombocytopenia per 10,000 pregnancies¹¹ and 5% of cases of pregnancy-associated thrombocytopenia⁸. It is the most common cause of significant thrombocytopenia in the first trimester. Concepts surrounding the mechanisms of thrombocytopenia in ITP have shifted from the traditional view of increased platelet destruction mediated by autoantibodies to more complex mechanisms in which both impaired platelet production and T-cell mediated effects play a role^{12,13}. The most common presentation is the finding of an asymptomatic thrombocytopenia on a routine blood count, when the distinction from GT may be difficult. Patients

occasionally present for the first time with severe thrombocytopenia in pregnancy, and women with previously diagnosed ITP often experience an exacerbation in pregnancy¹⁴. Symptomatic patients present with minor bruises or petechiae, bleeding from mucosal surfaces, or rarely fatal intracranial bleeding.

As in the non-pregnant patient, ITP is a diagnosis of exclusion with thrombocytopenia and normal or increased megakaryocytes in the bone marrow in the absence of other causes. There is no confirmatory laboratory test, and documentation of a low platelet count outside pregnancy is invaluable. Practically, however, in the absence of a platelet count prior to pregnancy, significant thrombocytopenia ($<100 \times 10^9/l$) in the first trimester, with a declining platelet count as gestation progresses, is most consistent with ITP. In contrast, mild thrombocytopenia developing in the second or third trimester and not associated with hypertension or proteinuria most likely represents GT¹⁵. Bone marrow examination is unnecessary unless there is suspicion of leukemia, lymphoma or malignant infiltration.

The decision to treat a pregnant woman with ITP is based on assessment of the risk of significant maternal hemorrhage. The count usually falls as pregnancy progresses, with a nadir in the third trimester¹⁴, and active treatment may have to be instituted to ensure a safe platelet count at the time of delivery. The incidence of antepartum hemorrhage is not increased in maternal ITP, but there is a small increased risk of PPH complications, not from the placental bed but from surgical incisions such as episiotomies and from soft-tissue lacerations¹⁶.

Asymptomatic patients with platelet counts $>20 \times 10^9/l$ do not require treatment until delivery is imminent but should be carefully monitored. Platelet counts of $>50 \times 10^9/l$ are regarded as safe for normal vaginal delivery, and those $>80 \times 10^9/l$ are safe for cesarean section, spinal or epidural anesthesia¹⁷.

The major treatment options for maternal ITP are corticosteroids or intravenous immunoglobulin (IVIg). There is no evidence, however, that either of these treatment modalities administered to the mother affects the platelet count in the fetus or neonate. If the duration of treatment is likely to be short, i.e. starting in the third trimester, corticosteroids are an effective option. An initial dose of 1 mg/kg prednisolone (based on pre-pregnancy weight) is recommended^{14,17}, which can be subsequently tapered. In addition to their toxicities in non-pregnant individuals, such as osteoporosis and weight gain, corticosteroids increase the incidence of pregnancy-induced hypertension and gestational diabetes, and may promote premature rupture of the fetal membranes.

Concerns about potential adverse maternal effects of steroids have led some to use IVIg as a first-line therapy in pregnancy^{15,18}. Others reserve this treatment for patients in whom steroid therapy is likely to be prolonged or in whom an unacceptably high maintenance dose is required (>7.5 mg prednisolone daily). The conventional dose of IVIg is 0.4 g/kg/day for

5 days, although 1 g/kg/day for 2 days has been used successfully and may be more convenient¹⁴. A persistent and predictable response is obtained in 80% of the cases. The response to therapy usually occurs within 24 h (more rapid than with steroids) and is maintained for 2–3 weeks. After an initial response, repeat single infusions can be used to prevent hemorrhagic symptoms and ensure an adequate platelet count for delivery.

Therapeutic options for those women with severely symptomatic ITP refractory to oral steroids or IVIg include high-dose intravenous methylprednisolone (1.0 g), perhaps combined with IVIg, or azathioprine¹⁷, but these should only be considered after careful assessment of the potential risks. Splenectomy is now rarely performed in pregnancy. It remains an option if all other attempts to increase the platelet count fail and is best performed in the second trimester. Approximately two-thirds of patients have a useful response to splenectomy. Prophylaxis against infections with organisms such as pneumococci, *Haemophilus influenzae* and *Neisseria meningitidis* is necessary. When splenectomy is performed during pregnancy, penicillin V prophylaxis should be given in the prenatal period, and vaccination against these organisms should be performed postnatally. Anecdotal reports exist of successful use of anti-D¹⁹ and of the anti-CD20 monoclonal antibody rituximab in pregnancy²⁰; however, until further studies are available, use of these agents in pregnancy should be restricted to refractory cases in which alternatives are unsuitable or have failed.

The offspring of mothers with ITP may also develop thrombocytopenia, as a result of the transplacental passage of maternal antiplatelet IgG^{8,15}. The incidence of severe neonatal thrombocytopenia ($<50 \times 10^9/l$) has been reported between 9 and 15%, with intracranial hemorrhage occurring in 0–1.5% of infants²¹. Due to the inability of maternal clinical characteristics to predict neonatal thrombocytopenia, antenatal (cordocentesis) and perinatal (fetal scalp blood sampling) procedures for determination of fetal platelet count have been considered in the past. Cordocentesis carries a mortality of 1–2%, however, whereas scalp blood sampling is associated with artifactually low results and risk of significant hemorrhage. For these reasons, both procedures are now largely abandoned in the management of ITP in pregnancy. The most reliable predictor of fetal thrombocytopenia is a history of thrombocytopenia at delivery in a prior sibling²².

In view of the very low risk of serious neonatal hemorrhage, it is now agreed that the mode of delivery in ITP should be determined by purely obstetric indications^{14,17}. If the maternal platelet count remains low at the time of delivery, despite optimal antenatal management, platelet transfusion may be required to treat maternal bleeding. Fetal scalp electrodes, fetal blood samples, ventouse delivery and rotational forceps should be avoided. Mothers with thrombocytopenia are unlikely to bleed from the uterine cavity

after the third stage of labor, provided that there are no retained products of conception. However, bleeding may occur from surgical wounds, episiotomies or perineal tears. Non-steroidal anti-inflammatory drugs should be avoided for postpartum analgesia. ITP should not exclude women from consideration for peripartum thrombosis prophylaxis. Prophylactic doses of low-molecular weight heparin (LMWH) are generally safe if the platelet count is greater than $50 \times 10^9/l$. Following delivery, a cord blood platelet count should be determined in all cases. Intramuscular injections, such as vitamin K, should be avoided until platelet count is known. Since the neonatal platelet count may decline for 4–5 days after delivery¹⁴, daily monitoring is indicated. Infants should be closely observed and treatment is rarely required. In those with clinical hemorrhage or platelet count $<20 \times 10^9/l$, treatment with IVIg produces a rapid response. Life-threatening hemorrhage should be managed with platelet transfusion combined with IVIg¹⁴.

Secondary autoimmune thrombocytopenia

Antiphospholipid syndrome

The diagnosis of primary antiphospholipid syndrome requires the coexistence of clinical manifestations (either vascular thrombosis or recurrent miscarriages) with laboratory evidence of reproducible antiphospholipid antibodies (either lupus anticoagulant or anticardiolipin antibody)²³. Primary antiphospholipid syndrome is associated with autoimmune thrombocytopenia in 20–40% of cases²⁴. Thrombocytopenia is rarely severe and usually does not require treatment. If treatment is necessary, management options during pregnancy are similar to those for primary ITP. However, primary antiphospholipid syndrome is associated with recurrent spontaneous abortions before 10 weeks of gestation, and women with the condition are at risk of intrauterine fetal growth restriction or death, pre-eclampsia and maternal thrombosis^{23,25}.

A combination of low-dose aspirin and prophylactic heparin is helpful in preventing recurrent spontaneous abortions in antiphospholipid syndrome²⁶. Antenatal and postnatal thrombosis prophylaxis is indicated in women with antiphospholipid syndrome and a history of thrombosis²⁷. Moderate thrombocytopenia should not alter decisions about antiplatelet or antithrombotic therapy in antiphospholipid syndrome²⁴.

Systemic lupus erythematosus

Immune platelet destruction may occur in systemic lupus erythematosus (SLE) because of antiplatelet antibodies or immune complexes, but thrombocytopenia is seldom severe; less than 5% of cases have a platelet count $<30 \times 10^9/l$ during the course of the disease¹⁶. Thrombocytopenia is often the first presenting feature and may precede any other manifestations of the condition by months or years. The management of isolated thrombocytopenia associated with SLE in pregnancy is governed by the principles outlined

for ITP. Women with SLE are also at risk for pre-eclampsia which may be complicated by thrombocytopenia.

HIV-associated thrombocytopenia

HIV-related thrombocytopenia can be caused by increased platelet destruction by antiplatelet antibodies or immune complexes, commonly during early-onset HIV. In advanced disease, drugs and infection may lead to marrow dysfunction that results in thrombocytopenia. In one series of HIV-positive women, approximately 3% were thrombocytopenic and, in most cases, thrombocytopenia was believed to be directly related to HIV infection²⁸. Slightly fewer than half of the thrombocytopenic women had a platelet count $<50 \times 10^9/l$, and 20% had hemorrhagic complications²⁸.

Treatment with antiretroviral therapy tends to improve the defective thrombopoiesis and increase the platelet count in HIV-positive patients, but some antiretroviral drugs may also cause thrombocytopenia. When immune destruction is believed to be a significant component of thrombocytopenia, IVIg may be required to treat hemorrhagic symptoms or to increase the platelet count before delivery in thrombocytopenic HIV-positive women²⁸. Corticosteroids are also effective but may be associated with increased risk of further immunosuppression and infection. Thrombotic thrombocytopenic purpura is found more frequently in HIV-infected patients and should be treated accordingly. Cesarean delivery reduces the risk of transmission of HIV from mother to fetus.

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia may be caused by immune- or non-immune-mediated platelet destruction or suppression of platelet production. Both are uncommon in pregnancy, but drug-induced causes should be considered and excluded. Drugs which are commonly associated with thrombocytopenia are shown in Table 3.

Heparin-induced thrombocytopenia A unique form of drug-induced thrombocytopenia is heparin-induced thrombocytopenia. It occurs in 1–5% of patients receiving unfractionated heparin but is considerably less common in patients treated with LMWH. Heparin-induced thrombocytopenia (HIT) is caused by an antibody directed against the heparin-platelet factor 4 complex, which can induce platelet activation and aggregation *in vivo*. Unlike other thrombocytopenias, HIT is complicated by arterial and/or venous thrombosis which may be life-threatening. Laboratory tests are available to confirm the diagnosis. HIT has been reported in pregnancy^{29,30}, although it may be less common in pregnant than in non-pregnant individuals³¹. Fetal thrombocytopenia does not occur because heparin does not cross the placenta. Heparin should be withdrawn immediately on clinical suspicion of HIT. If ongoing anticoagulation is

Table 3 Drugs causing thrombocytopenia

<i>Immune mediated</i>
Acetaminophen
Aminosalicylic acid
Amiodarone
Amphotericin B
Cimetidine
Diclofenac
Gold/gold salts
Levamisole
Methyldopa
Quinine and quinidine
Ranitidine
Sulfasalazine
Vancomycin
<i>Unique antibody-mediated process</i>
Heparin
<i>Suppression of platelet production</i>
Anagrelide
Valproic acid
<i>Suppression of all hematopoietic cells</i>
Chemotherapeutic agents

Adapted from George JN, Raskob GE, Shah SR, *et al.* Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998;129:886–90

urgently required, the heparinoid danaparoid may be used in most patients. Danaparoid has been used successfully to treat HIT in pregnancy³⁰. Hirudin is an alternative in non-pregnant patients, but experience is limited in pregnancy and its use is not recommended unless there is no suitable alternative³². Fondaparinux, a parenteral synthetic pentasaccharide which inhibits factor Xa indirectly, is not licensed for use in HIT but there are reports of its successful use in the management of HIT in pregnant women^{33,34}. Platelet transfusion should be avoided in patients with HIT. Routine monitoring of the platelet counts in pregnant women on prophylactic LMWH is no longer required because of the very low incidence of HIT in this situation^{35,36}, but regular monitoring is still required in pregnant women receiving unfractionated heparin (UFH)^{35,36}. British Committee for Standards in Haematology guidelines advise that the platelet count should be monitored in women receiving treatment doses of LMWH³⁵; however, the Royal College of Obstetricians and Gynaecologists venous thromboembolism guidelines recommend that monitoring is not necessary unless a woman has received UFH³⁶.

Thrombocytopenia with microangiopathy

Several syndromes are associated with thrombocytopenia as a result of platelet activation, red cell fragmentation and a variable degree of hemolysis (microangiopathic hemolytic anemia, MAHA). Some syndromes are unique to obstetric practice. The differential diagnosis is particularly pertinent for obstetricians and is important because management options differ. The differential diagnosis is summarized in Table 4.

Table 4 Differentiation of pregnancy-associated microangiopathies

Diagnosis	TTP	HUS	HELLP	Pre-eclampsia	AFLP
Time of onset	2nd trimester	Postpartum	3rd trimester	3rd trimester	3rd trimester
Hemolysis	+++	++	++	+	+
Thrombocytopenia	+++	++	++	++	+/ \pm
Coagulopathy	—	—	\pm	\pm	+++
Liver disease	\pm	\pm	+++	\pm	+++
Renal disease	\pm	+++	+	+	\pm
Hypertension	Rare	\pm	\pm	+++	\pm
CNS disease	+++	\pm	\pm	\pm	+
Effect of delivery on disease	None	None	Recovery	Recovery	Recovery
Management	Early plasma exchange	Supportive \pm plasma exchange	Supportive consider plasma exchange if persists	Supportive plasma exchange rarely required	Supportive

TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; HELLP, hemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy

Adapted from Horn EH. Thrombocytopenia and bleeding disorders. In: James DK, Steer PJ, Weiner CP, Gonik B, eds. *High-Risk Pregnancy: Management Options*, 3rd edn. Elsevier, 2006:901–24

Pre-eclampsia and HELLP syndrome

Pre-eclampsia affects approximately 6% of all pregnancies, most often those of primigravidas less than 20 or more than 30 years of age⁸. The criteria for the diagnosis include hypertension and proteinuria >300 mg/24 h developing after 20 weeks of gestation⁶. Although the clinical manifestations of pre-eclampsia generally do not become evident until the third trimester, the lesions underlying this disorder occur early in pregnancy and involve deficient remodeling of the maternal uterine vasculature by placental trophoblast cells^{37,38}. Thrombocytopenia develops in approximately 50% of patients, with the severity usually proportional to the severity of the pre-eclampsia. Occasionally, the onset of thrombocytopenia precedes other manifestations of pre-eclampsia⁸. Current understanding of the pathogenesis of thrombocytopenia in pre-eclampsia is that it is due to excessive platelet activation, adhesion of platelets to damaged or activated endothelium, and/or clearance of IgG-coated platelets by the reticuloendothelial system⁸.

Activation of the coagulation cascade occurs in most patients with pre-eclampsia; however, screening coagulation tests such as activated partial thromboplastin time (APTT), prothrombin time (PT) and fibrinogen are usually normal. Regardless, more sensitive markers of hemostatic activity such as D-dimer and TAT complexes are often elevated. In severe pre-eclampsia, the activation of coagulation results in consumption of clotting factors and therefore prolongation of the clotting test times and a fall in plasma fibrinogen.

The HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome is often considered to be a variant of pre-eclampsia and is the most common cause of severe liver disease in pregnant women³⁹. Criteria for the diagnosis of the HELLP syndrome include microangiopathic hemolytic anemia, aspartate aminotransferase (AST) more than 70 U/l and thrombocytopenia, with a platelet count less than $100 \times 10^9/l^{40}$. Patients may present with severe epigastric and right upper quadrant pain, which need not be accompanied by hypertension and proteinuria.

Exacerbation of HELLP syndrome may occur postpartum, and there is a recurrence risk of approximately 3% in subsequent pregnancies. The syndrome occasionally presents postpartum, usually within 48 h, but rarely as late as 6 days after delivery. Despite their similarities, HELLP is associated with significantly greater maternal and fetal morbidity and mortality than pre-eclampsia *per se*⁸.

Management of the pre-eclampsia/HELLP syndrome is supportive and should be focused on stabilizing the patient medically prior to early delivery of the fetus. Platelet transfusions may be needed if bleeding occurs or if thrombocytopenia is severe and cesarean delivery is planned, though the survival time of transfused platelets in patients with pre-eclampsia is diminished⁶. Regional analgesia is an option if the maternal platelet count is greater than $80 \times 10^9/l$ and the results of the coagulation screening tests are normal. If required, the consumptive coagulopathy resulting from pre-eclampsia should be treated with fresh frozen plasma (FFP). Consumptive coagulopathy severe enough to result in depletion of fibrinogen is uncommon in these disorders, but, if severe hypofibrinogenemia is present, plasma fibrinogen levels can be raised with cryoprecipitate or fibrinogen concentrate. In most cases, the clinical manifestations of pre-eclampsia resolve within several days after delivery, although the platelet count may decline for additional 24–48 h⁴¹. If severe thrombocytopenia, hemolysis or organ dysfunction persists after delivery, plasma exchange may be considered⁴², but the diagnosis should also be reviewed.

Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) share the central features of microangiopathic hemolytic anemia and thrombocytopenia. Though neither disease occurs exclusively during pregnancy, the incidence of both is increased in this setting, and up to 10% of all cases of TTP occur in pregnant patients⁶. TTP is defined by a pentad of symptoms that include MAHA,

thrombocytopenia, neurological abnormalities, fever and renal dysfunction, although the complete pentad is present at the time of diagnosis in less than 40% of patients⁴¹. The clinical manifestations of HUS are similar. Neurological abnormalities are a particular feature of patients with TTP; renal dysfunction is more severe in patients with HUS. Congenital or acquired deficiency of a specific von Willebrand factor-cleaving protease, ADAMTS 13, and the consequent increased level of high-molecular weight multimers of vWF play a central role in the pathogenesis of TTP. Interestingly, levels of ADAMTS 13 decrease during normal pregnancy, perhaps accounting, at least in part, for the predisposition to development of thrombotic microangiopathy in this setting⁴³.

TTP and HUS may be difficult to discern from one another, as well as from other pregnancy-associated microangiopathies such as pre-eclampsia or the HELLP syndrome. The extent of microangiopathic hemolysis is generally more severe in TTP or HUS than in pre-eclampsia or HELLP, and the former disorders are not associated with hypertension. The time of onset of these disorders is also helpful in differentiating between them. TTP usually presents in the second trimester, HUS in the postpartum period, and pre-eclampsia and the HELLP syndrome almost exclusively in the third trimester^{8,41,44}. Plasma antithrombin levels are normal in TTP and HUS and reduced in pre-eclampsia and HELLP⁴¹. Another feature distinguishing these disorders is their response to delivery. Whereas pre-eclampsia and the HELLP syndrome usually improve following delivery, the courses of TTP and HUS do not. Hence, pregnancy termination should not be considered therapeutic in patients with TTP or HUS⁴⁵. However, TTP responds equally well to plasma exchange in pregnant and non-pregnant patients with more than 75% of patients achieving remission⁶. Plasma exchange should be instituted as soon as possible after the diagnosis of TTP and should be continued daily until at least 48 h after complete remission is obtained. Repeated plasma exchange cycles are usually maintained until delivery. There is a rationale for use of immunosuppressive therapy in those patients with inhibitors of ADAMTS 13. The use of low dose aspirin has been advocated when the platelet count increases to more than $50 \times 10^9/l$. Platelet transfusion is contraindicated and may lead to rapid worsening of the condition. Management of HUS is supportive and includes renal dialysis and red cell transfusion. Plasma exchange has no proven benefit in the treatment of HUS.

The placental ischemia and increased incidence of premature delivery that complicate pregnancies in patients with TTP and HUS may lead to poor fetal outcomes, but these are markedly improved by good management of the conditions.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) affects one of every 5000–10,000 pregnancies and is most common

in primagravidas during the third trimester⁴⁶. The cause of the condition is unknown in the majority of instances, but some patients may have a long-chain 3-hydroxy-acyl CoA dehydrogenase (LCHAD) deficiency⁴⁷.

Patients present with overt signs of hepatic damage and may have hemorrhagic manifestations, perhaps the result of decreased synthesis of clotting factors and consumptive coagulopathy. Evidence for consumptive coagulopathy is provided by thrombocytopenia, prolonged APTT and PT, and by decrease in fibrinogen and antithrombin levels.

AFLP is most aptly viewed as part of the pregnancy-associated microangiopathies; up to 50% of patients with AFLP may also meet criteria for pre-eclampsia. The extent of microangiopathic hemolysis and thrombocytopenia is generally mild compared with that observed in HELLP, TTP, or HUS⁴⁸.

Delivery is the most important aspect of management, as it starts the reversal of the pathological process. Coagulation defects are managed supportively with FFP, cryoprecipitate or fibrinogen concentrate and platelet concentrates. In these patients, normalization of hemostatic abnormalities may not occur for up to 10 days after delivery. Fetal mortality in this disorder approaches 15%, though maternal mortality occurs in less than 5% of cases⁴⁶.

CONSUMPTIVE COAGULOPATHY

Disseminated intravascular coagulation (DIC) is an acquired clinicopathologic syndrome, characterized by activation of the coagulation system, and resulting in widespread intravascular deposition of fibrin-rich thrombi. Consumption of clotting factors usually leads to a bleeding diathesis, although a small percentage of affected individuals may go on to develop widespread thrombosis with peripheral organ ischemia. *Some degree of consumptive coagulopathy accompanies most forms of obstetric hemorrhage; however, the greater risk of coagulopathy usually arises from consumption of clotting factors and platelets as a result of massive obstetric hemorrhage. The combination of massive hemorrhage and coagulation failure is recognized as one of the most serious complications in pregnancy.*

Obstetric consumptive coagulopathy is usually acute in onset (except as an uncommon late complication of retained dead fetus) and can be caused by a variety of disease processes. It is triggered by several mechanisms including release of TF into the circulation, endothelial damage to small vessels and production of procoagulant phospholipids in response to intravascular hemolysis⁴⁹ (Table 5). Blood loss itself with transfusion and volume replacement may also trigger consumptive coagulopathy. When obstetric complications are associated with coagulation failure, several mechanisms may interact. These triggers lead to the generation of thrombin, cause defects in inhibitors of coagulation and suppress fibrinolysis. Thrombin promotes platelet activation and aggregates formation, which occlude the microvasculature and

Table 5 Mechanism of consumptive coagulopathy in pregnancy

<i>Injury to vascular endothelium</i>	
Pre-eclampsia	
Hypovolemic shock	
Septicemic shock	
<i>Release of tissue factor (TF)</i>	
Placental abruption	
Amniotic fluid embolism	
Retained dead fetus	
Placenta accreta	
Acute fatty liver	
<i>Production of procoagulant</i>	
Fetomaternal hemorrhage	
Phospholipids	
Incompatible blood transfusion	
Septicemia	
Intravascular hemolysis	

From Anthony J. Major obstetric hemorrhage and disseminated intravascular coagulation. In: James DK, Steer PJ, Weiner CP, Gonik B, eds. *High-Risk Pregnancy: Management Options*, 3rd edn. Elsevier, 2006:1606–23

result in thrombocytopenia. Thrombin becomes bound to antithrombin (AT) and thrombomodulin, and these proteins are soon consumed. Following binding to thrombomodulin, thrombin activates the anticoagulant protein C, which also becomes depleted, predisposing to microvascular thrombosis. In consumptive coagulopathy secondary to sepsis, increased levels of C4b-binding protein result in the binding of more free protein S, and therefore render it unavailable to be a cofactor of the anticoagulant protein C. PAI-1 is increased out of proportion to the level of tissue plasminogen activator (tPA), resulting in depressed fibrinolysis. Fibrin is formed, but its removal is impaired, leading to thrombosis of small and middle-size vessels. The passage of erythrocytes through partially occluded vessels leads to red cell fragmentation and microangiopathic hemolytic anemia.

Placental abruption is the most common cause of obstetric consumptive coagulopathy (60% of cases; 5% of all abruptions), but the syndrome is uncommon unless the abruption is severe enough to cause fetal death. Initially, increased intrauterine pressure forces TF-rich decidual fragments into the maternal circulation. However, in severe abruption, hypovolemic shock, large volume transfusion and high levels of fibrin degradation products (FDPs) that act as anticoagulants themselves exacerbate the situation. Retained dead fetus may cause chronic consumptive coagulopathy by release of TF from the dead fetus into the maternal circulation, but generally only if the fetus is at least of 20 weeks' size and the period of death is more than 4 weeks. Amniotic fluid embolism occurs during labor, cesarean section or within a short time of delivery. Amniotic fluid is rich in TF and may enter uterine veins when there has been a tear in the uterine wall. The condition may lead to maternal death as a result of severe pulmonary hypertension following embolization of the pulmonary vessels by fetal squames. If the mother survives this acute event, there may be an

anaphylactoid reaction to the presence of the fetal tissues in the maternal circulation associated with cardiovascular collapse, pulmonary edema and the development of consumptive coagulopathy.

Sepsis causes consumptive coagulopathy via the release of proinflammatory cytokines such as tumor necrosis factor α (TNF α), interleukin 1 (IL-1) and IL-6, which may trigger TF expression by monocytes and endothelial cells⁵⁰. Severe pre-eclampsia with intense vasospasm and resulting ischemia causes endothelial injury and expression of TF.

Acute consumptive coagulopathy in pregnancy presents almost invariably with bleeding – either as a genital tract bleeding from the placental site or bleeding from the wound after cesarean section. There may be excessive bleeding from venepuncture sites.

Laboratory investigations are essential to establish the diagnosis of consumptive coagulopathy. The characteristic changes are a low or falling platelet count and a prolongation of the APTT and PT. Fibrinogen level falls with the progression of the coagulopathy; the normal range in late pregnancy is 4–6 g/l which is significantly higher than the non-pregnant range, 2–4 g/l; coagulation fails at levels of less than 1 g/l. FDPs are increased, reflecting the excessive deposition of fibrin and enhanced fibrinolysis. The D-dimer is the most commonly used parameter to assess FDP levels, as it is specific for fibrin breakdown. Normal D-dimer levels are below 200 ng/ml, but often exceed 2000 ng/ml in cases of consumptive coagulopathy. The blood film may show evidence of microangiopathic hemolysis with fragmentation of red cells.

The basic principles in treatment of consumptive coagulopathy are removal of the precipitating cause if possible, correction of aggravating factors, and replacement of missing coagulation factors and platelets. Any etiological condition should be promptly treated; delivery of the fetus is often required. Correction of aggravating factors such as shock and hypoxia is important. This includes red cell transfusion if necessary and oxygen administration. Intravenous antibiotics should be given if sepsis is suspected. Replacement of clotting factors is most effectively performed with FFP at a dose of 15–20 ml/kg. If there is severe hypofibrinogenemia, cryoprecipitate or virally inactivated fibrinogen concentrate may be required; two cryoprecipitate pools (10 donor units) or 3–5 g of fibrinogen concentrate are expected to raise plasma fibrinogen by approximately 1 g/l. Platelets should be maintained above $50 \times 10^9/l$ in the presence of active bleeding by the administration of blood group-compatible platelets. Heparin use often leads to excessive bleeding and therefore does not usually have a role in obstetric consumptive coagulopathy except in cases of a retained dead fetus. Similarly, antifibrinolytic drugs (tranexamic acid, aprotinin) are not helpful and are usually contraindicated because they inhibit the removal of deposited fibrin by fibrinolysis.

The D-dimer, platelet count and fibrinogen level are clinically useful tests in monitoring replacement therapy if the patient is bleeding. The aim should be to

achieve a platelet count above $50 \times 10^9/l$, a fibrinogen level of more than 1.0 g/l and significant shortening of the APTT and PT to approach their normal values.

Although recombinant activated factor VII (rFVIIa) is not licensed for use in pregnancy, it has been used in obstetric patients with consumptive coagulopathy and severe bleeding not responsive to other treatment options^{51,52}. Consumptive coagulopathy is not a contraindication to the use of rFVIIa if massive bleeding is occurring. However, caution should be used in patients with major consumptive coagulopathy because there are occasional reports of thrombosis and consumptive coagulopathy after the use of rFVIIa⁵³.

Recombinant activated protein C (raPC) has been successfully used in sepsis-related obstetric consumptive coagulopathy at a dose of 24 $\mu\text{g}/\text{kg}/\text{h}$ in a 96 h infusion^{54,55}. Caution is needed in patients with severe thrombocytopenia ($<30 \times 10^9/l$) because of the increased incidence of intracerebral hemorrhage associated with its use; monitoring platelet count and platelet transfusion as necessary are important considerations. In addition to acting as an anticoagulant, raPC has direct anti-inflammatory and anti-apoptotic properties⁵⁶. This may explain in part why the other endogenous anticoagulants (antithrombin and TFPI) used in severe sepsis have not shown such good efficacy.

FACTOR VIII INHIBITORS

Acquired hemophilia is due to the development of an autoantibody to factor VIII (FVIII). The estimated incidence is approximately 1 per 1,000,000 per annum. Most cases occur in healthy individuals without discernible risk factors, but the condition is associated with autoimmune disorders such as rheumatoid arthritis and SLE, inflammatory bowel disease, multiple sclerosis and malignancies. In up to 11% of cases, the associated factor is a recent or ongoing pregnancy⁵⁷.

Acquired hemophilia may occur in relation to any pregnancy, but the risk appears to be greatest after the first delivery. Onset is usually at term or within 3 months postpartum, but may only become evident 12 months postdelivery⁵⁸. Clinical manifestations do not necessarily correlate with inhibitor levels and can range from spontaneous bruising to life-threatening hemorrhage. FVIII inhibitors may cross the placenta and persist in the neonate for up to 3 months, but neonatal complications are rare⁵⁸. Spontaneous resolution occurs in almost 100% of women first diagnosed in the postpartum period after 30 months⁵⁷.

Basic coagulation studies in acquired hemophilia demonstrate a prolonged APPT with a normal PT and thrombin time (TT). If plasma from the patient is mixed with normal plasma, the APPT remains prolonged due to the inhibitor antibody neutralizing the FVIII in the normal plasma. FVIII inhibitors must be differentiated from a lupus inhibitor by specific tests because the clinical implications are profoundly

different. Quantification of FVIII inhibitor is by the Bethesda assay, and checking this level may help in determining the choice of therapy and monitoring the progress of the patient.

Treatment is aimed at control of bleeding and accelerating the elimination of inhibitors. Hematological measures to minimize blood loss aim to compensate for the loss of FVIII. Choice of product to attempt to normalize hemostasis depends on various considerations, including the severity of bleeding, availability of clotting factor concentrates, inhibitor level and cross-reactivity of inhibitor to porcine FVIII. Human FVIII may be effective if the titer of inhibitor is low, i.e. less than 10 Bethesda units. At higher levels, use of porcine FVIII which may not cross-react with the inhibitor, and rFVIIa or prothrombin complex concentrate (PCC) become necessary⁵⁹.

Inhibiting the production of the inhibitor is the second management aim. Prednisolone at a dose of 1 mg/kg is associated with a loss of inhibitor in 50% of patients with acquired hemophilia⁵⁹. Other immunosuppressives should be considered if there is no response to steroids. Addition of cyclophosphamide (2–3 mg/kg) should be considered at 3 weeks if there is no decline in the inhibitor titer, or earlier if there is continued bleeding. Other methods to reduce inhibitor levels include azathioprine or infusion of IVIg; plasma exchange is rarely effective. Rituximab has been used in the management of postpartum acquired hemophilia⁶⁰.

ANTICOAGULANT THERAPY DURING PREGNANCY AND THE PERIPARTUM PERIOD

Anticoagulant therapy is indicated during pregnancy for the prevention and treatment of venous thromboembolism (VTE), for the prevention and treatment of systemic embolism in patients with mechanical heart valve prostheses and, in combination with aspirin, for the prevention of recurrent pregnancy loss in women with antiphospholipid syndrome (APS) or other thrombophilias.

The anticoagulants currently available for the prevention and treatment of VTE and arterial thromboembolism include UFH, LMWH, vitamin K antagonists and direct thrombin and factor Xa inhibitors. Among these, heparins and warfarin are the principal drugs. The novel oral anticoagulants, direct inhibitors of thrombin and factor Xa, are promising but their role is not established and there are no data on their use in pregnancy.

Heparins are the anticoagulant of choice during pregnancy for situations in which their efficacy is established. Neither UFH nor LMWH cross the placenta⁶¹. Heparins are not associated with any known teratogenic risk, and the fetus is not anticoagulated as a result of maternal heparin use. LMWHs have potential advantages over UFH during pregnancy because they have a longer plasma half-life and a more predictable dose-response than UFH, with the potential for once-daily administration. In addition, LMWHs are

associated with a lower risk of HIT and osteoporosis than UFH.

Coumarin derivatives such as warfarin cross the placenta and have the potential to cause teratogenicity as well as to anticoagulate the fetus predisposing to bleeding *in utero*. It is probable that oral anticoagulants are safe during the first 6 weeks of gestation, but there is an approximately 5% risk of developmental abnormalities of fetal cartilage and bone if they are taken between 6 and 12 weeks' gestation⁶². The risk of warfarin embryopathy is dose dependent, with an increased risk when the daily warfarin dose exceeds 5 mg⁶³. Fetal intracranial bleeds *in utero* are a well-established complication after exposure to these drugs during any trimester. In general, coumarins should not be used for the prevention or treatment of VTE in pregnancy, but they remain the anticoagulants of choice for the management of pregnant women with mechanical heart valve prostheses.

Fondaparinux is used for prophylaxis and treatment of VTE and treatment of acute coronary syndrome (ACS). It is not licensed for use in pregnancy, but there are reports of its successful use in the management of VTE in pregnant women³³.

LMWHs are currently widely used for the prevention and treatment of gestational VTE. In our institution, women on prophylactic doses of LMWH are advised to have the dose of the LMWH tailed off at the end of pregnancy and omit their dose if labor is suspected. Women on a therapeutic dose of LMWH are admitted in advance of planned induction to be converted to the therapeutic dose of intravenous UFH. They should omit LMWH on the day of admission and should be started on UFH, aiming for an APTT ratio of 1.5–2.0. UFH should be reduced to 500 IU/h when contractions start, aiming for an APTT ratio of less than 1.5 and should be stopped at the second stage of labor or earlier if a cesarean section may be required. In the latter case, protamine sulfate may be needed for reversal of UFH if the APTT ratio remains above 1.5. Postpartum, the heparin infusion can be restarted 4 h postdelivery at 500 IU/h, providing there is no bleeding. Patients are restarted on a therapeutic dose of LMWH 2–3 days after delivery. Warfarin can be started 4–5 days postpartum, and LMWH should be continued until an international normalized ratio (INR) of 2.0 or greater is reached on two consecutive days. Breastfeeding is safe on UFH, LMWH and warfarin.

Epidural anesthesia is generally safe in women following discontinuation of UFH, providing their coagulation screen is normal and their platelet count is more than $80 \times 10^9/l$. It remains unclear what period of time should elapse between the last dose of LMWH and insertion or removal of an epidural or spinal catheter, or how long the time interval should be until the next dose. The guidelines of the Royal College of Obstetricians and Gynaecologists suggest that, in women on treatment dose of LMWH, 24 hours should elapse after the last dose of the LMWH before insertion of an epidural catheter or spinal catheter, the

cannula not to be removed within 12 hours of the most recent injection, and no further dose of LMWH should be given for at least 4 hours after its removal³⁶. For women on prophylactic doses of LMWH, regional anesthetic techniques should not be used until 12 hours have elapsed since the last injection. As above, the cannula should not be removed within 12 hours of the most recent injection, and no further dose of LMWH should be given for at least 4 hours after its removal.

Women with mechanical heart valve prostheses require anticoagulation throughout pregnancy. They have a high thrombotic risk with older type of mechanical prostheses (e.g. Starr-Edwards or Bjork-Shiley), a prosthesis in the mitral position, multiple prosthetic valves, atrial fibrillation and a history of previous thrombotic event.

On the other hand, women with newer less thrombogenic bileaflet valves, particularly if they are in the aortic position (and providing they are in sinus rhythm and have normal left ventricular function), may be regarded as being at lower thromboembolic risk.

There is controversy surrounding the optimal choice of anticoagulation in pregnant women with mechanical heart valve prostheses. Both LMWH and UFH have been associated with an increased incidence of valve thrombosis compared with warfarin⁶⁴.

Despite the fetal consequences associated with oral anticoagulation, the European Society of Cardiology recommends warfarin as the anticoagulant of choice for pregnant women with mechanical heart valve prostheses⁶⁵. UFH may be considered during the first trimester; warfarin is then used with a switch to UFH at 36 weeks to decrease the risk of fetal bleeding complications at delivery.

The American College of Chest Physicians recommends one of three anticoagulant regimens consisting of UFH, LMWH, or warfarin with UFH or LMWH during the first trimester and at the end of pregnancy, in women with mechanical heart valves⁶¹. The lack of well designed trials does not allow identification of one approach as clearly superior to others.

Decisions about the most appropriate anticoagulant regimen during pregnancy for women with mechanical heart valve prostheses must be made on an individual patient basis after careful counseling, and should be based as much as possible on the relative risks of the various thromboprophylaxis regimens and whether the patient is perceived to be at high or low thromboembolic risk.

On the basis of the report that the risk of fetal complications with warfarin appears to be dose-related, providing their daily warfarin requirement does not exceed 5 mg⁶³, some women may feel reassured about the relatively low risk to their fetus if they use warfarin throughout pregnancy, or with substitution of UFH or LMWH from 6 to 12 weeks' gestation. However, women whose daily warfarin requirement exceeds 5 mg, particularly if they are classified into the lower thromboembolic risk group, may wish to minimize

the risk of fetal complication and may be prepared to rely on adjusted doses of LMWH. The peak anti-Xa level 4 hours postinjection should be between 1.0 and 1.2 U/ml⁶¹.

CONGENITAL DISORDERS OF HEMOSTASIS

Congenital platelet disorders

Bernard–Soulier syndrome is a rare autosomal recessive platelet disorder due to a variety of mutations in membrane glycoproteins Ib, IX and V. Patients usually present early in life with spontaneous bruising, epistaxis or bleeding after minor trauma; menorrhagia is a common presentation. Laboratory findings include thrombocytopenia, large platelets, prolonged bleeding time and poor platelet aggregation *in vitro* to ristocetin.

In a review of 30 pregnancies in 18 women with Bernard–Soulier syndrome, primary PPH was reported in 10 pregnancies (33%) and secondary PPH in 12 pregnancies (40%)⁶⁶. Options for management of bleeding in Bernard–Soulier syndrome in pregnancy include tranexamic acid, desmopressin (DDAVP), rFVIIa and platelet transfusion. It is preferable to avoid platelet transfusion if at all possible because of its associated risk of alloantibody formation; maternal alloantibodies can cross the placenta and cause fetal or neonatal alloimmune thrombocytopenia. In the above review, alloimmune thrombocytopenia was reported in six neonates, with one intrauterine death and one neonatal death. The use of rFVIIa combined with tranexamic acid is recommended for uncomplicated vaginal delivery. However, HLA-matched platelet infusion with tranexamic acid is recommended as a first line treatment for cesarean sections or if bleeding occurs during vaginal delivery.

Regional analgesia is contraindicated because of the risk of spinal/epidural hematoma. The safest mode of delivery for the fetus and the mother is controversial. In most of the reported cases, cesarean section was the preferred mode of delivery. PPH has been reported in patients delivered vaginally and by cesarean section. However, the risk of bleeding to the fetus is only in association with alloimmune thrombocytopenia. If this diagnosis is excluded, cesarean section should be reserved for obstetric indications. When vaginal delivery is contemplated, prolonged labor especially during the second stage and instrumental deliveries should be avoided.

Glanzmann's thrombasthenia is due to a spectrum of mutations in platelet membrane GP IIb/IIIa, resulting in failure to bind fibrinogen. It is characterized by excessive menstrual blood loss, bleeding from mucous membranes, and major hemorrhage following trauma or surgery. The platelet count is normal, but clot retraction is greatly impaired and agents such as adenosine diphosphate (ADP), epinephrine and collagen fail to induce platelet aggregation. In a review of 31 detailed case reports of 40 pregnancies in 35 women with Glanzmann's thrombasthenia, antenatal bleeding was described in 50% of pregnancies but was

usually mild and occurred at mucocutaneous sites⁶⁷. Primary PPH was reported in 34% of the pregnancies and secondary PPH in 24%. PPH was frequently severe and occurred up to 20 days after delivery. There was a wide variation in approach to prevention and treatment of PPH, but most women received platelet transfusion, sometimes with additional rFVIIa and antifibrinolytics. Maternal alloimmunization against platelets was reported in 73% of pregnancies and was associated with four neonatal deaths⁶⁷. Regional anesthesia is contraindicated in Glanzmann's thrombasthenia. Elective cesarean section was performed in 31% of the reported pregnancies, but there was no discernible relationship between this mode of delivery and the frequency of maternal or fetal bleeding. Many centers would now consider elective cesarean section in mothers with Glanzmann's thrombasthenia for obstetric indications or in situations of high fetal bleeding risk such as maternal alloimmunization.

The May–Hegglin anomaly is a rare autosomal dominant condition with thrombocytopenia and giant platelets. Platelet count varies between 40 and $80 \times 10^9/l$, but platelet function appears normal. Excess hemorrhage is uncommon, but patients may need a platelet transfusion to achieve hemostasis at delivery⁶⁸.

von Willebrand disease

von Willebrand disease (vWD) is the most common of the inherited bleeding disorders, reportedly found in approximately 1% of the general population without ethnic variations. It is caused by a reduced plasma concentration of structurally normal von Willebrand factor (vWF) or the presence of a structurally abnormal molecule with reduced activity. vWF is the carrier protein in plasma for FVIII, and it also acts as a bridge between platelets and subendothelial collagen fibers.

vWF is synthesized in endothelial cells as a polypeptide of 2813 amino acids, which undergoes initial dimerization and then multimerization up to a multimer with a molecular weight of 20,000 kDa. High-molecular weight (HMW) multimers are functionally more effective in promoting platelet adhesion and aggregation. The vWF protein is stored in Weibel–Palade bodies in the endothelial cells from where it is released into the plasma. vWF is also synthesized in megakaryocytes, stored in the platelet α -granules and, on activation, secreted by the platelet release reaction. This allows accumulation of vWF at the site of vascular injury where it can promote further platelet adhesion and thus hemostasis. The mature vWF protein possesses a number of specific binding sites, which represent its different activities (Figure 1). Circulating HMW multimers are cleaved by a protease, known as ADAMTS 13, which is lacking in patients with the rare congenital thrombotic thrombocytopenic purpura.

vWD is subclassified into seven categories (Table 6), which correspond to distinct pathophysiological

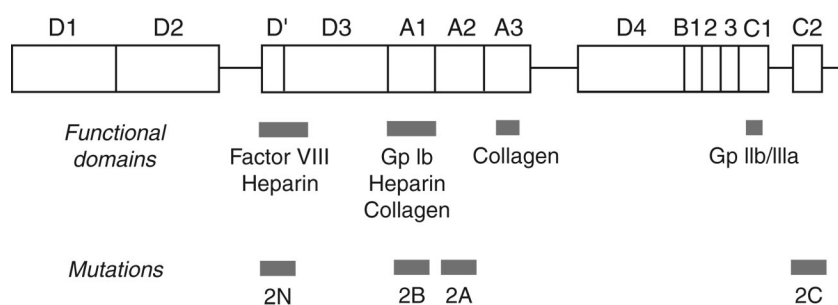


Figure 1 The von Willebrand factor. The protein consists of a series of domains with different binding sites for factor VIII, heparin, collagen and platelet glycoprotein (Gp) Ib and IIb/IIIa. The sites of gene mutations giving rise to different subtypes of VWD are marked. From Green D, Ludlam CA. VWD in bleeding disorders. *Health Press* 2004:63–9

mechanisms and are important in determining therapy. Of all the categories, about approximately 70–80% of patients have type 1 disease.

The condition commonly presents as a mild to moderate bleeding disorder, typically with easy bruising or bleeding from mucosal surfaces. The most frequent problem found in the non-pregnant female is menorrhagia, which may be quite severe. Patients with mild abnormalities may be asymptomatic, with the diagnosis made only after significant hemostatic challenges such as operations and trauma.

Laboratory tests in patients with vWD reveal a prolonged bleeding time and may show a prolonged APTT. More definitive diagnostic tests depend on the finding of reduced vWF activity measured by ristocetin cofactor activity (vWF:RCo) and collagen-binding assay (vWF:CB), accompanied by variable reductions in vWF antigen (vWF:Ag) and FVIII. Several further tests that aid in classification include analysis of ristocetin-induced platelet aggregation (RIPA), vWF multimer and assay of FVIII binding to vWF⁶⁹. Mild thrombocytopenia may occur in patients with vWD type 2B.

The diagnosis may not be straightforward, as one or more of the activities of FVIII and vWF may be borderline and even normal. It is often necessary to repeat the estimations on at least three occasions. Stress, physical exercise, recent surgery and pregnancy all increase plasma vWF and FVIII levels, and diagnosis may be difficult in these circumstances⁷⁰. When investigating patients with borderline results, it should be taken into account that FVIII and vWF levels are 15–20% lower in individuals with blood group O compared to individuals with blood group A⁷⁰. Molecular genetic analysis may be useful as an aid to diagnosis in type 2 or 3 vWD. Knowledge of the mutation may also aid genetic counseling and allow the option of prenatal diagnosis to be offered to women at risk of having a child with severe type 3 vWD.

The aim of therapy for vWD is to correct impaired primary hemostasis and impaired coagulation. Treatment choice depends on the severity and the type of disease, and on the clinical setting. Treatment options usually include DDAVP and vWF-containing blood products⁷¹.

Table 6 Classification of von Willebrand disease (vWD)

Type 1	Partial quantitative deficiency of apparently normal vWF
Type 2	Qualitative deficiency of vWF
Type 2A	Qualitative variants with decreased HMW multimers
Type 2B	Qualitative variants with increased affinity for platelet GP Ib
Type 2M	Qualitative variants with normal HMW multimers appearance
Type 2N	Qualitative variants with markedly decreased affinity for factor VIII
Type 3	Virtually complete deficiency of vWF

vWF, von Willebrand factor; HMW, high-molecular weight

Adapted from Sadler JE. *Thromb Haemost* 1994;71:520–5

DDAVP, a synthetic vasopressin analogue, releases vWF from endothelial stores; it also increases plasma FVIII level. It is usually given by slow intravenous infusion of 0.3 µg/kg over 20 min, which can be repeated every 4–6 h on two or three occasions. The drug can also be given subcutaneously or as a nasal spray. Side-effects include hypotension, facial flushing, fluid retention for up to 24 h and consequent hyponatremia. DDAVP can safely be used during pregnancy and after delivery^{72,73}. It is effective in many situations in type 1 vWD in which a 3–5-fold increase in the plasma vWF and FVIII levels could be seen. It is of no therapeutic benefit in type 3 vWD because of the very low basal levels of vWF and FVIII. The response in type 2s is less predictable. DDAVP is contraindicated in patients with type 2B because it may exacerbate the co-existing thrombocytopenia. Patients should have a test of DDAVP (if possible when not pregnant) to see if it increases the vWF/ FVIII level sufficiently to prevent or stop hemorrhage.

Plasma-derived vWF containing concentrates are necessary in patients who do not respond adequately to DDAVP or in whom it is contraindicated. The loading dose is 40–60 IU/kg, and this can be followed by repeat doses every 12–24 h to maintain vWF activity (vWF:RCoF) more than 50%. All currently available concentrates are derived from plasma. As at least one viral inactivation step is included in their manufacture, they are unlikely to transmit hepatitis or HIV, but there is still a risk of parvovirus infection.

von Willebrand disease and pregnancy

von Willebrand disease is the most common congenital hemostatic disorder in pregnancy. In a normal pregnancy, both FVIII and vWF levels progressively increase (Figure 2)⁷⁴. vWF starts to rise as early as the 6th week and by the third trimester may have increased 3–4-fold. FVIII and vWF levels also increase in most women with vWD, which may explain the frequent improvement in minor bleeding manifestations during pregnancy. The hemostatic response to pregnancy depends on both the type and severity of disease. Most women with type 1 vWD have an increase in FVIII and vWF levels into the normal non-pregnant range, which may mask the diagnosis during pregnancy. However, levels may remain low in severe cases. FVIII and vWF antigen levels often increase in pregnant women with type 2 vWD with minimal or no increase in vWF activity levels. In type 2B vWD, the increase in the abnormal vWF can cause progressive and severe thrombocytopenia, but intervention is not usually required. Most women with type 3 vWD have no improvement in FVIII or vWF levels during pregnancy⁷⁵. After delivery, FVIII and vWF in normal women fall slowly to baseline levels over a period of 4–6 weeks. As the individual hemostatic response to pregnancy is variable, vWF and FVIII levels should be checked at booking, 28 weeks', 34 weeks' gestation and prior to invasive procedures⁷³. vWF and FVIII levels may fall rapidly after delivery and should be checked a few days postpartum.

Antepartum hemorrhage is uncommon in women with vWD, but may occur after spontaneous miscarriage or elective termination, occasionally as the initial presentation of vWD. The risk of bleeding in patients with vWD is usually greatest postpartum; PPH may be the first presentation of vWD. One series showed an 18.5% incidence of primary PPH and a 20% incidence of secondary PPH⁷⁶. The risk is greater in women with type 2 and 3 disease and those whose FVIII and vWD levels are less than 50%. vWD may also exacerbate bleeding due to other obstetric causes, such as uterine atony or a trauma to the birth canal. Other

pregnancy-associated reasons for bleeding in women with vWD include extensive bruising and hematomas at intramuscular injection, episiotomy and surgical wound sites.

For patients whose vWD profile has normalized in pregnancy, no specific hemostatic support is required. For patients whose vWF activity (vWF:RCO) has not normalized, hemostatic supportive therapy is necessary to cover vaginal delivery or cesarean section. Treatment is indicated to raise FVIII level and vWF activity above 50%⁷⁶. Patients with type 1 vWD may receive DDAVP if they are responsive and there are no current contraindications; patients with type 2 and 3 vWD will usually require vWF concentrate.

Ventouse delivery, fetal blood sampling and fetal scalp electrodes should be avoided if the fetus is at risk for type 2 or 3 vWD or more severe forms of type 1 vWD. Because of the high incidence of secondary PPH in patients with vWD, efforts should be made to ensure that the placenta is complete upon expulsion or removal. Careful and prompt repair of episiotomy wounds or perineal tears is advisable.

Decisions about regional analgesia should be individualized⁷⁷. In type 1 vWD when FVIII and vWF activity have spontaneously corrected, epidural anesthesia is likely to be safe. Alternatives should be used for patients with type 2 or 3 vWD and in type 1 vWD where vWF activity has remained low, as bleeding in such cases does not always correlate with laboratory parameters after corrective treatment.

After delivery, all patients should be closely observed for PPH and uncorrected hemostatic defects treated. In responsive patients, DDAVP is the treatment of choice to prevent and treat mild to moderate postpartum bleeding. FVIII level and vWF activity should be maintained at greater than 50% for 3 days following vaginal delivery and for 5–7 days following cesarean section.

It is difficult and unnecessary to diagnose type 1 or type 2 vWD in the neonate. If type 3 vWD is suspected, a cord blood sample should be sent for assay of FVIII and vWF activity. Intramuscular injections should be avoided for both mother and newborn.

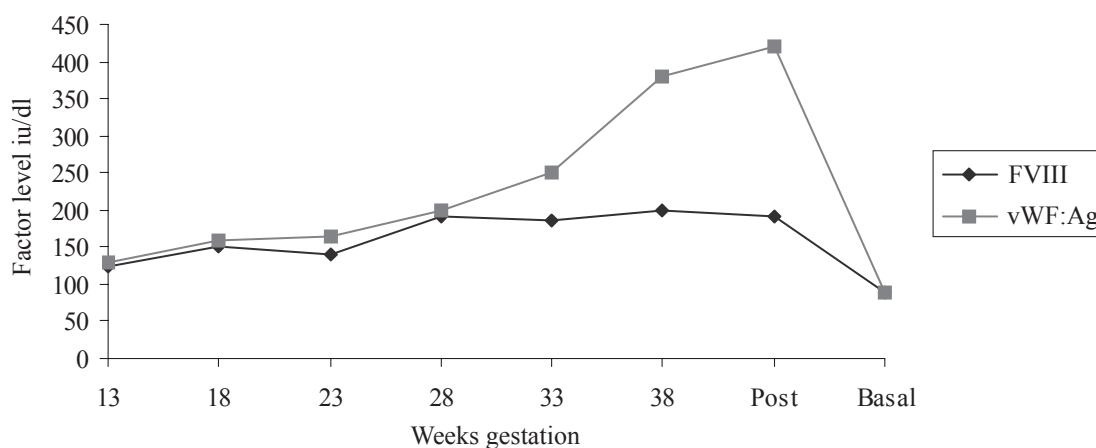


Figure 2 Levels of factor VIII and vWF in normal pregnancy. From Giangrande PL. Management of pregnancy in carriers of haemophilia. *Haemophilia* 1998;4:779–84

HEMOPHILIAS

Hemophilias A and B are the most common severe congenital bleeding disorders associated with reduced or absent coagulation FVIII and FIX, respectively. Hemophilia A affects approximately one in 5000 live male births and hemophilia B affects approximately one in 30,000 live male births. The genes for both conditions are located on the X-chromosome; they are therefore sex-linked disorders that almost exclusively affect males. Clinically, the hemophilias cause a spectrum of bleeding manifestations varying from easy bruising to spontaneous deep muscle and joint hemorrhages and intracranial bleeding. Hemophilias can only be distinguished by measuring plasma levels of the specific clotting factors. The clinical severity is directly related to plasma concentrations of FVIII/FIX. Individuals with levels of below 1% of normal have severe hemophilia and the most frequent bleeds. Females in families with a history of hemophilia may be obligate, potential or sporadic carriers, depending on the details of the pedigree⁷⁸. An obligate carrier is a woman, whose father has hemophilia, or a woman who has family history of hemophilia and who has given birth to a hemophilic son, or a woman who has more than one child with hemophilia. A potential carrier of hemophilia is a woman who has a maternal relative with the disorder. A woman with one affected child and no family history is likely to be a sporadic carrier⁷⁸. Female carriers of hemophilia are expected to have clotting factor levels around 50% of normal as they have only one affected chromosome. However, a wide range of values (5–219%)⁷⁹ has been reported as a result of random inactivation of the X-chromosomes (lyonization). If the FVIII/IX level is less than 50%, abnormal bleeding may occur after trauma or surgery.

There are two main risks for a female carrier of hemophilia in pregnancy. First, women with a low FVIII/IX level may be at risk of bleeding after delivery or during invasive procedures in the first trimester. Second, there is a 50% chance of each son inheriting hemophilia and 50% of her daughters being carriers.

As discussed earlier, the levels of FVIII tend to increase during normal pregnancy (Figure 2). The increase is particularly marked during the third trimester, when levels of FVIII may rise to double the normal baseline value. Similarly, the vast majority of carriers of hemophilia A will have increased their FVIII production to within the normal range by late gestation; factor replacement therapy is thus only rarely required during delivery in carriers of hemophilia A. The risk of bleeding in carriers of hemophilia A is greatest in the postpartum period because FVIII levels may decrease rapidly after delivery. By contrast, the level of FIX does not increase significantly during pregnancy, and thus a woman with a low initial baseline FIX is more likely to require replacement to control bleeding complications during delivery.

All women who are obligate or potential carriers of hemophilia should be offered genetic testing and counseling. In particular, they should have their carrier

status determined to allow for the optimal management of their pregnancies. Genetic testing should be offered when the individual is able to understand the issues concerned (usually at age of 13–15 years) and after having given informed consent⁸⁰. In many individuals in the UK with hemophilia A and B, the causative mutation has been identified. If the mutation within the family is known, it is straightforward to screen the potential carrier. If, on the other hand, the mutation is not known, then linkage analysis using informative genetic polymorphisms may be possible. If neither of these approaches is suitable, then direct mutation detection may be possible by sequencing the FVIII/FIX gene.

Coagulation studies should also be carried out to identify carriers with low FVIII/FIX levels. Phenotypic data may be helpful in assessing the statistical risk of carriership if molecular diagnosis is not possible. However, normal levels of FVIII/FIX do not exclude carrier status⁸⁰. Women who have low levels of FVIII may have a useful hemostatic response to DDAVP. To establish whether this response is occurring, a trial of DDAVP can be attempted, with measurement of the response in FVIII levels over the next 24 h.

Once carrier status has been established, women should be offered pre-pregnancy counseling to provide them with the information necessary to make informed reproductive choices. Preimplantation diagnosis is potentially useful for carriers of hemophilia who, after counseling, do not wish to contemplate bringing up a hemophilic child, but would not consider termination of an affected fetus. Following *in vitro* fertilization (IVF) treatment, it is possible to remove a single embryonic cell at the 8–16-cell stage and carry out genetic diagnosis. Female or unaffected male embryos can then be transferred into the uterus. In the UK, each such test requires a license from the Human Fertilisation and Embryology Authority.

If prenatal diagnosis is requested and a suitable molecular marker exists, testing is usually carried out by chorionic villus sampling (CVS) at 11–12 weeks; DNA extracted from fetal cells is analyzed. The principal advantage of this procedure is that it may be applied during the first trimester, so that, if termination of the pregnancy is required, this is easier to accomplish. The main adverse event related to CVS is miscarriage, which is estimated at about 1–2%. Cells as a source of DNA can also be obtained from amniotic fluid (amniocentesis) after 15 weeks' gestation; here, the miscarriage rate is about 0.5–1%. Fetal blood sampling by cordocentesis is now rarely carried out because of the inherent hazards associated with this procedure. The use of prenatal diagnosis is decreasing in developed countries; as hemophilia care improves, more couples are willing to contemplate bringing up a child with hemophilia⁷⁴.

Fetal sex should be determined in all pregnancies in which the fetus is at risk of hemophilia. Non-invasive determination of fetal gender is now possible in the first trimester by ultrasound and/or analysis of free fetal DNA in maternal blood and has been shown to be a

reliable method of avoiding invasive prenatal diagnostic tests in pregnancies⁸¹. Women may not wish to know the sex of the infant as they would not consider termination of pregnancy. However, this information is important for the appropriate management of labor and delivery.

Factor VIII/IX levels in female carriers of hemophilia should be monitored regularly in pregnancy. UK guidelines recommend measurement of coagulation factor levels at booking, at 28 weeks and at 34 weeks⁷³. It is particularly important to measure coagulation factor levels toward the end of the third trimester (34–36 weeks) to plan management of delivery⁷⁴. If maternal FVIII/FIX levels remain low at 34–36 weeks in hemophilia carriers, treatment is necessary for delivery⁷⁴. FVIII/FIX plasma levels should be maintained at greater than 50% for all modes of delivery⁷³. Epidural anesthesia may be used if coagulation defects have been corrected and the relevant factor level is above 50% or has been raised to more than 50%⁷³. Recombinant FVIII/FIX or DDAVP (for carriers of hemophilia A only) should be used. Plasma-derived factor concentrate products, including those subjected to dual inactivation processes, have the potential to transmit non-lipid coated viruses, e.g. parvovirus, and should be avoided if possible. Recombinant FVIII/FIX concentrates avoid the risk of potential viral transmission. Infection of the fetus with parvovirus may result in hydrops fetalis and fetal death.

The optimal mode of delivery for a fetus at risk of hemophilia remains the subject of debate due to continuing uncertainty regarding the risk of intracranial (ICH) and extracranial hemorrhage (ECH). In a recently published population based study, infants of maternal carriers of hemophilia were more often delivered by cesarean section⁸². In the same survey, 17 cases of intracranial hemorrhage were reported, two of which were associated with assisted delivery, while 14 followed spontaneous vaginal delivery and one followed emergency cesarean delivery. In cases of vaginal delivery, ventouse delivery is absolutely contraindicated because of the risk of major cephalohematoma and intracranial bleeding. Mid-cavity rotational forceps delivery should be avoided, but simple lift-out forceps delivery is allowed. Fetal scalp sampling and scalp electrodes should not be used if the fetus may have hemophilia.

Most bleeding problems in carriers of hemophilia occur postpartum. In a series of 65 live births in 53 carriers of hemophilia the incidence of primary and secondary PPH was reported at 19% and 2%, respectively, compared with 5% and 0.7%, respectively, in the general population⁸¹. Replacement therapy should be given immediately after delivery to mothers with an uncorrected hemostatic defect. Treatment options at this stage are the same as those during labor and delivery. Supportive therapy to maintain hemostasis should be continued for at least 3 days after vaginal delivery and for at least 5 days after cesarean section⁷³.

Cord blood should be obtained for FVIII/FIX assay⁸³. In the infant, intramuscular injections should be avoided until hemophilia has been excluded. Both

ICH and ECH are observed in newborn infants with hemophilia and the incidence of ICH in neonates with severe hemophilia is estimated to be 1–4%⁸³. Routine cranial ultrasound scan may be a useful screening investigation, but cannot be relied upon to detect all cases of early ICH. In neonates with non-specific symptoms which could represent ICH, or in neonates with a documented ECH, computed tomography (CT) or MRI scanning should be considered even in the presence of an apparently normal cranial ultrasound scan. Where there is a strong clinical suspicion of ICH or other bleeding, factor concentrate should be given immediately and not withheld pending definitive imaging studies.

RARE COAGULATION DISORDERS

Inherited abnormalities of fibrinogen

Inherited abnormalities of fibrinogen consist of quantitative (afibrinogenemia and hypofibrinogenemia) and qualitative deficiencies (dysfibrinogenemia). Afibrinogenemia refers to a total absence of fibrinogen, while hypofibrinogenemia is a milder form of the disorder with a decreased level of both antigenic and functional (Clauss) fibrinogen. These conditions can also coexist as hypodysfibrinogenemia. In normal pregnancy fibrinogen levels may increase to up to two-fold from non-pregnant levels, whereas the hemostatic abnormality in women with fibrinogen deficiency/dysfunction is expected to continue throughout pregnancy. Afibrinogenemia is an autosomal recessive disorder in contrast to hypofibrinogenemia which can be inherited as either a dominant or a recessive trait. Both are associated with recurrent miscarriages as well as placental abruption and PPH⁸⁴.

In women with afibrinogenemia, regular replacement therapy throughout pregnancy to keep fibrinogen levels above 1 g/l is recommended and should be commenced as soon as possible in pregnancy to prevent early fetal loss⁸⁵. Replacement therapy may be required in women with hypofibrinogenemia depending on the fibrinogen level and the bleeding tendency. Options for replacement therapy include plasma-derived fibrinogen concentrate and cryoprecipitate. Cryoprecipitate is a good source of fibrinogen but should not usually be used, as it is not virally inactivated. Fibrinogen concentrate is heat treated and the preferred option. Fibrinogen clearance increases as the pregnancy progresses and the amount of the infused fibrinogen will need to increase with advancing gestation. Thrombotic events have also been reported in patients with inherited afibrinogenemia⁸⁴; hence, the risk of bleeding and thrombosis should be considered and balanced during pregnancy.

For labor and delivery, in women with afibrinogenemia, replacement therapy to maintain a minimum fibrinogen level of 1.5 g/l has been suggested for the prevention of placental abruption and PPH⁸⁵. For women with hypofibrinogenemia, intrapartum replacement is required if the fibrinogen level is below

1.5 g/l and/or if the woman has a significant bleeding history⁸⁴.

Afibrinogenemia and hypofibrinogenemia are associated with a high risk of PPH. In a literature review of congenital hypofibrinogenemia, PPH was found to be the most common obstetric complication occurring in 45% (14/31 deliveries) among 10 patients⁸⁶. Paradoxically thrombotic events during puerperium have also been reported in afibrinogenemia and hypofibrinogenemia⁸⁴. The postpartum management of these patients should take into account any personal and family history of bleeding and thrombosis. Standard measures such as compression stockings, adequate hydration and early mobilization are recommended.

Dysfibrinogenemia is inherited as an autosomal dominant trait and the diagnosis is made by demonstrating a low functional fibrinogen with a normal antigenic fibrinogen. This condition has an unpredictable clinical phenotype; as such, the management of pregnant women with dysfibrinogenemia needs to be individualized, taking into account the fibrinogen level and personal and family history of bleeding and thrombosis. In asymptomatic women no specific treatment is required during pregnancy. Women with a personal or family history of thrombosis should be offered antenatal thromboprophylaxis with LMWH; fibrinogen replacement is given only if bleeding occurs. Conversely, replacement therapy should be considered in women with a personal or family bleeding phenotype, and concomitant thromboprophylaxis with LMWH should also be considered as fibrinogen may precipitate venous thrombosis⁸⁷.

Women with dysfibrinogenemia are also at risk of both postpartum thrombosis and hemorrhage; therefore, their intrapartum and postpartum management should be individualized. In asymptomatic women or those with a mild bleeding phenotype, no specific treatment other than close observation is required. Vaginal delivery can be managed conservatively with treatment given to raise fibrinogen level to more than 1 g/l above baseline if bleeding occurs. However, if the bleeding tendency is significant or if the woman is undergoing cesarean section, prophylactic treatment is recommended to raise the fibrinogen level to more than 1 g/l baseline and to maintain it above 0.5 g/l until wound healing has occurred⁸⁷. Standard measures for venous thrombosis should be followed in all women with dysfibrinogenemia. Postpartum thromboprophylaxis with LMWH is recommended for those with personal or family history of thrombosis or following cesarean section as such surgery is usually performed under replacement cover⁸⁷.

As dysfibrinogenemia is usually transmitted as an autosomal dominant trait, it is important to regard the neonate as potentially affected and avoid invasive monitoring procedures and instrumental deliveries.

Factor VII deficiency

Congenital FVII deficiency is the most common of the rare inherited coagulation disorders with an

estimated prevalence of 1 in 500,000. It is inherited in an autosomal recessive manner and its frequency is significantly increased in countries where consanguineous marriages are common. FVII levels are usually less than 10% in homozygotes and around 50% in heterozygotes. Although there is a poor correlation between FVII levels and bleeding risk, hemorrhages occur in patients with factor VII levels below 10%⁸⁴. Individuals with a moderate FVII deficiency often bleed from the mucous membranes, and epistaxis, bleeding gums and menorrhagia are common. In severe FVII deficiency (FVII level <2%), bleeding into the central nervous system very early in life leads to a high morbidity and mortality. Congenital FVII deficiency is usually suspected when an isolated prolongation of the PT is found in a patient without liver disease, and a normal APTT and fibrinogen level.

A significant rise in FVII level is seen during pregnancy in non-deficient women. This has also been observed in women with mild/moderate forms of FVII deficiency (heterozygotes)⁸⁸ but not in women with severe deficiency⁸⁹. In women with mild/moderate deficiency, FVII level may normalize at term; therefore, replacement therapy may not be required for labor and delivery. However, this decision should be individualized and should take into account the mother's bleeding history, FVII level in the third trimester and the mode of delivery. Women with FVII level of less than 10–20% at term or significant bleeding history are more likely to be at risk of PPH and require prophylactic treatment⁸⁹.

Recombinant activated FVII (rFVIIa) has been approved in the European Union for use in congenital FVII deficiency⁹⁰. In places where this product is not available, FFP, PCC or plasma-derived FVII concentrate may be used. Recombinant FVIIa is given in boluses of 20 µg/kg; higher doses may be associated with thrombosis.

Factor V deficiency

Hereditary FV deficiency is a very rare autosomal recessive condition. The prevalence of the homozygous state is approximately 1 in 1,000,000. Parental consanguinity is often present. In homozygote individuals, FV levels range from less than 1% to 10% and in heterozygotes FV level is around 50%⁸⁷. FV deficiency is associated with prolongation of both the PT and the APTT, but a normal TT and is confirmed by performing a FV assay. Homozygous deficiency is associated with a moderately severe bleeding disorder in the form of easy bruising and mucous membrane bleeding, but patients may also develop hemarthroses and muscle hematomas. Pregnancy and delivery are not usually accompanied by any bleeding complications in women with FV levels of around 50%. Women with FV deficiency especially those with low FV levels appear to be at increased risk of PPH. In women with partial (heterozygous) deficiency and no history of bleeding, labor and delivery could be managed expectantly⁸⁷. However, in women with

severe (homozygous) deficiency substitution therapy with FFP (as no FV concentrate is available) is recommended to raise FV level above 15–25%⁸⁴. Further doses may be necessary to maintain these levels during and after delivery. If cesarean section is performed, it is recommended that FV levels are maintained above this level until wound healing is established⁸⁷.

Combined factor V and VIII deficiency

Combined FV and FVIII deficiency is a rare autosomal recessive disorder which usually arises as a consequence of consanguinity. It is caused by mutations in one of two different genes, LMAN1 and MCFD2, which encode proteins that form a complex involved in the transport of FV and FVIII from the endoplasmic reticulum to the Golgi apparatus. Although mild bleeding symptoms such as easy bruising and epistaxis are not uncommon in affected individuals, circulating levels of FV and FVIII are usually sufficient to prevent more severe spontaneous bleeding episodes. The combined deficiency disorder is associated with a prolongation of both the PT and the APTT, with the APTT prolongation disproportionate to that of the PT. Factor assays reveal levels of between 5 and 20% for both FV and FVIII⁹¹. There are no published data on the management of pregnant women with this combined deficiency. As FV levels in pregnancy do not change significantly and FVIII levels rise throughout the pregnancy, any possible bleeding, especially during labor and delivery, is likely to be dependent on the FV level. However, both levels should be monitored with FV levels kept above 15–20% and FVIII levels above 50% during delivery or for any invasive procedures⁸⁷.

Factor X deficiency

Congenital FX deficiency is an autosomal recessive disorder. The prevalence of the severe (homozygous) form is 1 in 1,000,000 in the general population and is much higher in countries where consanguineous marriages are more common. The prevalence of heterozygous FX deficiency is about 1:500, but individuals are usually clinically asymptomatic. Severe FX deficiency (FX level <1%) is associated with a significant risk of intracranial hemorrhage in the first weeks of life and umbilical stump bleeding. The most frequent symptom is epistaxis, which is seen with all severities of deficiency. Menorrhagia occurs in half of the women. Severe arthropathy may occur as a result of recurrent joint bleeds. Mild deficiency is defined by FX levels of 6–10%; these individuals are often diagnosed incidentally, but may experience easy bruising or menorrhagia. The diagnosis of FX deficiency is suspected following the finding of a prolonged APTT and PT and is confirmed by measuring plasma FX levels.

Fourteen pregnancies in nine women with isolated FX deficiency have been reported in the literature⁹². The complications described include spontaneous abortions, placental abruptions, premature births and PPH. FX levels increase during pregnancy and

antenatal replacement therapy is not usually needed. However, women with severe FX deficiency and a history of adverse outcome in pregnancy may benefit from aggressive replacement therapy⁸⁷. FX is present in PCCs. FFP may be an alternative when PCCs are not available. As the half-life of FX is 24–40 h, a single daily infusion is usually adequate. FX levels of 10–20% are generally sufficient for hemostasis⁸⁷ and are required at the time of delivery. FX levels should be monitored as caution is required because of the prothrombotic properties of these concentrates.

Combined deficiencies of the vitamin K-dependent factors II, VII, IX and X

Congenital combined deficiency of factors II, VII, IX and X is an autosomal recessive bleeding disorder. It is caused by deficiency of enzymes associated with vitamin K metabolism (e.g. γ -glutamyl carboxylase) as a result of homozygous genetic mutations. Mucocutaneous and postoperative related bleeding have been reported. Severe cases may present with intracranial hemorrhage or umbilical cord bleeding in infancy. Some individuals have associated skeletal abnormalities (probably related to abnormalities in bone vitamin K-dependent proteins such as osteocalcin). Severe bleeding is usually associated with activities of the vitamin K-dependent factors of less than 5%. Affected individuals show prolongation of the APTT and PT associated with variable reductions in the specific activities of factors II, VII, IX and X.

The clinical picture and response to vitamin K is variable, some responding to low-dose oral vitamin K, but others are non-responsive even to high-dose intravenous replacement. In those individuals who are non-responsive to vitamin K, PCCs are the product of choice.

There is a single report of a pregnancy progressing to term in an individual with severe congenital vitamin K-dependent clotting factor deficiency managed with oral vitamin K 15 mg daily throughout pregnancy. Bleeding from an episiotomy wound in this case required fresh frozen plasma⁹³.

Factor XI deficiency

FXI deficiency is an autosomally inherited condition, which is particularly common in Ashkenazi Jews in whom heterozygote frequency is 8%. Overall, the prevalence of severe deficiency is approximately 1 in 1,000,000, but partial deficiency is much more common. The deficiency is classified as severe if the FXI level is less than 15% (homozygotes) and as partial at 15–70% (heterozygotes); the lower limit of the normal range is 70%. It is associated with a variable bleeding tendency, and bleeding can occur in heterozygous as well as homozygous individuals. Spontaneous bleeding is extremely rare, even in those with undetectable FXI levels. Bleeding is provoked by injury or surgery, particularly in areas of high fibrinolytic activity (e.g. genitourinary tract). Menorrhagia is common, and

women with FXI deficiency may be diagnosed as a consequence of this. The bleeding tendency can be inconsistent with an individual and the family, and could not clearly be related to the factor levels. This unpredictable nature of FXI deficiency makes management for pregnancy and delivery difficult. The APTT is usually prolonged and diagnosis is confirmed by finding a low FXI level.

As FXI level does not increase during pregnancy, many women will continue to have a subnormal factor level at term, and thus be at risk of excessive bleeding during delivery. Women with FXI deficiency are also at increased risk of both primary and secondary PPH. In a case series of 11 women with FXI deficiency, the incidence of primary and secondary PPH was 16% and 24%, respectively⁷⁶.

Due to the unpredictable bleeding tendency in FXI deficiency, the decision for prophylaxis during labor and delivery needs to be individualized and must take into consideration FXI level, personal/family bleeding history and the mode of delivery. In women with partial FXI deficiency and no bleeding history but previous hemostatic challenge, treatment is not usually required during vaginal delivery. In women with partial deficiency and significant bleeding history or no previous hemostatic challenges, tranexamic acid is often used for 3 days, with the first dose being administered during labor. Tranexamic acid is also used to manage prolonged mild intermittent secondary PPH which is a common presentation of FXI-deficient patients⁹⁴. FXI concentrate is needed for severely deficient women to cover vaginal delivery and also for cesarean section. The aim is to maintain the FXI level between 50% and 70% during labor and for 3–4 days after vaginal delivery and 7 days after cesarean section. FXI concentrate is potentially thrombogenic; the single dose should not exceed 30 IU/kg with the aim of raising FXI level to no greater than 70%⁹⁴. Concurrent use of tranexamic acid or other antifibrinolytic drugs with FXI concentrate should be avoided. FFP can be used, but in patients with severe deficiency, it is difficult to produce a sufficient rise (to more than 30%) without the risk of fluid overload⁸⁷. Recombinant FVIIa has been used successfully to manage adult patients with FXI deficiency undergoing surgery, although it is not licensed for this indication⁸⁷.

Factor XIII deficiency

Congenital FXIII (fibrin stabilizing factor) deficiency is an autosomal recessive disorder. FXIII circulates in plasma as a tetramer composed of two A-subunits and two B-subunits. There are three types of FXIII deficiency: type I is a combined deficiency of both subunits A and B, type II is a deficiency of subunit A and type III is a deficiency of subunit B⁸⁴.

The condition is characterized by features of delayed and impaired wound healing with bleeding occurring 24–36 h after surgery or trauma. Umbilical bleeding in the first few weeks of life is very suggestive of the disorder. Soft tissue bleeds are more common

than hemarthroses, which usually only occur after trauma. Spontaneous intracranial bleeds are a characteristic feature. The severity of the bleeding state varies markedly between individuals with apparently similar FXIII plasma levels. The routine tests (APTT and PT) are normal and the FXIII level has to be specifically requested of the laboratory.

Women with types I and III usually conceive and deliver normally, whereas the majority of women with type II deficiency miscarry without appropriate replacement therapy started preconception. Regular therapy to maintain the FXIII level at more than 3%⁸⁷ and if possible more than 10%⁹⁵ is recommended to prevent bleeding and pregnancy loss in women with type II deficiency. A FXIII level of more than 20%, and if possible, more than 30% during labor/delivery has been suggested to minimize the risk of bleeding complications⁹⁵. FXIII concentrate, either plasma-derived or recombinant, is the treatment of choice and is superior to FFP and cryoprecipitate. FXIII has a half-life of 7–10 days and therefore only needs to be given at 4–6-weekly intervals.

The incidence of PPH in women with FXIII deficiency is not known. Successful pregnancy in women with FXIII subunit A deficiency is generally only achieved with replacement therapy throughout pregnancy and at delivery⁹⁵ and as the administered FXIII concentrate has a long circulating half-life most of these cases are not complicated by PPH. Women with types I and III FXIII deficiency usually conceive and deliver normally without replacement therapy, but PPH and postpartum prophylaxis should be considered in these cases.

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