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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 procoagulant and help prevent excessive bleeding at the time of delivery. The concentrations of coagulation factors V, VII, VIII, IX, X, XII 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 XIII levels tend to decrease in late pregnancy after an initial increase in the beginning of 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 procoagulant effect[1]. Although concentrations of soluble tissue factor (TF) remain constant during normal pregnancy[2], monocyte TF activity and expression are lower when compared with those in non-pregnant women, possibly acting to counterbalance the procoagulant 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 state[5].

Although the overall balance shifts towards hypercoagulability, 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.

Table 1 Coagulation system changes in normal pregnancy

	Increased	*Decreased*	*No change*
Systemic changes			
Procoagulant factors	I, V, VII, VIII, IX, X, XII	XIII	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		
Local placental changes	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. Adapted from Brenner B. Haemostatic changes in pregnancy. *Thromb Res* 2004;114:409–14

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 to 400×10^9/l, and thrombocytopenia is defined as a count of less than 150×10^9/l. The platelet count may decline by approximately 10% during normal pregnancy[6]. Spontaneous bleeding is unusual unless the count has fallen to below 30×10^9/l, but surgical bleeding or postpartum hemorrhage may occur as a consequence of platelets less than 50×10^9/l. Thrombocytopenia in pregnancy may result from 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 artefact due to EDTA-induced platelet aggregation *in vitro* and can be diagnosed by visual inspection of the blood film, when platelet changes are readily visible.

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[7,8]. 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[7,8]. It is an entirely benign condition, which 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 100×10^9/l, the diagnosis must be reviewed. Rare cases, subsequently confirmed as GT, have had counts as low as 50×10^9/l[9]. Epidural anesthesia is considered safe if the maternal platelet count is greater than 80×10^9/l. Delivery should proceed according to obstetric indications and the cord platelet count should be checked. GT is difficult to distinguish from idiopathic thrombocytopenic purpura, when thrombocytopenia is identified for the first time during pregnancy and no previous counts have been documented.

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) accounts for one to five cases of thrombocytopenia per 10 000 pregnancies[10] and 5% of cases of pregnancy-associated thrombocytopenia[7]; it

Table 2 Causes of pregnancy-associated thrombocytopenia

Pregnancy-specific	*Not pregnancy-specific*
Gestational (incidental) thrombocytopenia	Idiopathic thrombocytopenic purpura (ITP)
Pre-eclampsia	Thrombotic thrombocytopenic purpura (TTP)
HELLP syndrome (hemolysis, elevated liver enzymes and low platelets)	Hemolytic uremic syndrome (HUS)
	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

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

is the most common cause of significant thrombocytopenia in the first trimester. ITP is characterized by premature clearance of platelets by antiplatelet antibodies and consequent increased production of platelets by the bone marrow. 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 pregnancy[11]. 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 the third trimester and not associated with hypertension or proteinuria most likely represents GT[12]. 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 trimester[11], 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 postpartum hemorrhagic complications, not from the placental bed but from surgical incisions such as episiotomies and from soft-tissue lacerations[13].

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 anesthesia[14].

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 pregnancy weight) is recommended[11,14], 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[15,16]. 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 convenient[11]. 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 azathioprine[14], 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.

The offspring of mothers with ITP may also develop thrombocytopenia, as a result of the

transplacental passage of maternal antiplatelet IgG[7,12]. 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 infants[17]. 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 artefactually 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 sibling[18].

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[11,14]. 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. 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 are generally safe if the platelet count is greater than 50×10^9/l. Following delivery, a cord blood platelet count should be determined in all cases. Since the neonatal platelet count may decline for 4–5 days after delivery[11], 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 IVIg[11].

Secondary autoimmune thrombocytopenia

Antiphospholipid syndrome

The diagnosis of primary antiphospholipid syndrome requires the coexistence of clinical manifestations (either vascular thrombosis or pregnancy morbidity) with laboratory evidence of reproducible antiphospholipid antibodies (either lupus anticoagulant or anticardiolipin antibody)[19]. Primary antiphospholipid syndrome is associated with autoimmune thrombocytopenia in 20–40% of cases[20]. 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[19,21].

A combination of low-dose aspirin and low-dose subcutaneous heparin is helpful in preventing recurrent spontaneous abortions in antiphospholipid syndrome[22]. Antenatal and postnatal thrombosis prophylaxis is indicated in women with antiphospholipid syndrome and a history of thrombosis[23]. Moderate thrombocytopenia should not alter decisions about antiplatelet or antithrombotic therapy in antiphospholipid syndrome[20].

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 platelet count $< 30 \times 10^9$/l during the course of the disease[13]. Thrombocytopenia is often the first presenting feature and may precede any other manifestations of the condition by months or years. It is difficult to document any special effect of pregnancy on SLE; the general consensus is that pregnancy does not affect the long-term prognosis of SLE, but that pregnancy itself may be associated with more flare-ups, particularly in the puerperium[24]. 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 infection[25]. Slightly fewer than half of the thrombocytopenic women had a platelet count $< 50 \times 10^9$/l, and 20% had hemorrhagic complications[25].

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 women[25]. 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.

A unique form of drug-induced thrombocytopenia is heparin-induced thrombocytopenia (HIT). It occurs in 1–5% of patients receiving unfractionated heparin but is considerably less common in patients treated with low-molecular weight heparins. 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[26,27], although it may be less common in pregnant than in non-pregnant individuals[28]. 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 urgently required, the heparinoid danaparoid may be used in most patients. Danaparoid has been used successfully to treat HIT in pregnancy[27]. Hirudin is an alternative in non-pregnant patients, but experience is limited in

Table 3 Drugs causing thrombocytopenia

A. *Immune mediated*
Acetaminophen
Aminosalicylic acid
Amiodarone
Amphotericin B
Cimetidine
Diclofenac
Gold/gold salts
Levamisole
Methyldopa
Quinine and quinidine
Ranitidine
Sulfasalazine
Vancomycin
B. *Unique antibody-mediated process*
Heparin
C. *Suppression of platelet production*
Anagrelide
Valproic acid
D. *Suppression of all hematopoietic cells*
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

pregnancy and its use is not recommended unless there is no suitable alternative[29]. Platelet transfusion should be avoided in patients with HIT. Because HIT is potentially life-threatening, all women must have a platelet count before treatment with heparin begins. The count must be repeated on day 4 of first exposure to heparin or day 1 of repeat exposure and then at least weekly for the first 3 weeks.

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.

Pre-eclampsia and HELLP syndrome

Pre-eclampsia affects approximately 6% of all pregnancies, most often those of primigravidas less than 20 or greater than 30 years of age[7]. The criteria for the condition include hypertension and proteinuria > 300 mg/24 h developing after 20 weeks of gestation[6]. 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 remodelling of the maternal uterine vasculature by placental trophoblast cells[30,31]. 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-eclampsia[7]. 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 system[7].

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.

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	+++	++	++	++	+/±
Coagulopathy	-	-	±	±	+++
Liver disease	±	±	+++	±	+++
Renal disease	±	+++	+	+	±
Hypertension	rare	±	±	+++	±
CNS disease	+++	±	±	±	+
Effect of delivery on disease	none	none	recovery	recovery	recovery
Management	early plasma exchange	supportive ± 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

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 women[32]. Criteria for the HELLP syndrome include microangiopathic hemolytic anemia, aspartate aminotransferase (AST) > 70 U/l and thrombocytopenia, with a platelet count $< 100 \times 10^9$/l[33]. 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[7].

Management of 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 diminished[6]. 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. 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 h[34]. If severe thrombocytopenia, hemolysis or organ dysfunction persists after delivery, plasma exchange may be considered[35], but the diagnosis should also be reviewed.

Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome

Thrombotic thrombocytopenia (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 patients[6].

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 patients[34]. The clinical manifestations of HUS are similar. Neurological abnormalities are particularly a 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 setting[36].

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[7,34,37]. Plasma antithrombin levels are normal in TTP and HUS and reduced in pre-eclampsia and HELLP[34]. 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 HUS[38]. However, TTP responds equally well to plasma exchange in pregnant and non-pregnant patients with > 75% of patients achieving remission[6]. Plasma exchange should be instituted as soon as possible after the diagnosis of TTP. Daily plasma exchange should continue until at least 48 h after complete remission is obtained.

Repeated plasma exchange cycles are usually maintained until delivery. 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 these conditions.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy affects one of every 5000–10 000 pregnancies and is most common in primagravidas during the third trimester[39]. 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) deficiency[40].

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 to that observed in HELLP, TTP, or HUS[41].

Delivery is the most important aspect of management, as it starts the reversal of the pathological process. Coagulation defects are managed supportively with fresh frozen plasma, cryoprecipitate 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 cases[39].

CONSUMPTIVE COAGULOPATHY

Consumptive coagulopathy (disseminated intravascular coagulation) 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 hemolysis[42] (Table 5). Blood loss

Table 5 Mechanism of consumptive coagulopathy in pregnancy

A. *Injury to vascular endothelium*
Pre-eclampsia
Hypovolemic shock
Septicemic shock
B. *Release of tissue factor (TF)*
Placental abruption
Amniotic fluid embolism
Retained dead fetus
Placenta accreta
Acute fatty liver
C. *Production of procoagulant*
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

itself with transfusion and volume replacement may also trigger consumptive coagulopathy. With obstetric complications associated with coagulation failure, there may be interaction of several mechanisms.

These triggers lead to the generation of thrombin, cause defects in inhibitors of coagulation and suppress fibrinolysis. Thrombin promotes platelet activation and aggregates form, which occlude the microvasculature and 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 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 cells[43]. 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 < 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 under 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. 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 done with fresh frozen plasma.

If there is severe hypofibrinogenemia, cryoprecipitate may be required. Platelets should be maintained $> 50 \times 10^9$/l in the presence of active bleeding by the administration of blood group-compatible platelets. Any etiological condition should be promptly treated; it often requires delivery of the fetus. Heparin use often leads to excessive bleeding and therefore does not usually have a role in obstetric consumptive coagulopathy except in the 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 usual regimen, when there is coagulation failure in obstetric practice, includes administration of FFP, platelets and cryoprecipitate. FFP contains fibrinogen and all coagulation factors. Each unit is approximately 250 ml and the usual requirement is 4–6 units. Platelet concentrates are used to increment platelet count. A unit of platelets is approximately 60 ml in volume; it should raise the platelet count by 5000×10^9/l and the usual dose is five packs. Cryoprecipitate is enriched in fibrinogen, factor VIII and vWF and is particularly useful for the treatment of hypofibrinogenemia. Ten bags (each 30 ml) of cryoprecipitate should increase the fibrinogen level by 1 g/l. One 250 ml unit of FFP contains a similar amount of fibrinogen (500 mg) as one 30 ml bag of cryoprecipitate (435 mg).

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 $> 50 \times 10^9$/l, a fibrinogen level > 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[44,45] (see Chapter 26). 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 rFVIIa[46].

Recombinant activated protein C (raPC) has been successfully used in sepsis-related obstetric consumptive coagulopathy at a dose of 24 μg/kg/h in a 96-h infusion[47,48]. 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 of the platelet count and transfusion of platelets as necessary are important considerations. In addition to acting as an anticoagulant, raPC has direct anti-inflammatory and anti-apoptotic properties[49]. This may explain in part why the other endogenous anticoagulants (antithrombin and tissue factor pathway inhibitor) used in severe sepsis have not shown such good efficacy.

The treatment of such underlying conditions such as abruptio placentae, uterine rupture and fetal death require immediate obstetric attention. Usually, there has been extensive hemorrhage and red cell transfusion is needed in addition to correction of the coagulation failure.

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 conditions 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 pregnancy[50].

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 post-delivery[51]. 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 rare[51]. Spontaneous resolution occurs in almost 100% of women first diagnosed in the postpartum period after 30 months[50].

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 recombinant FVIIa or prothrombin complex concentrate (PCC) becomes necessary[52].

Inhibiting the production of the inhibitor is the second management aim. Prednisolone at dose of 1 mg/kg is associated with a loss of inhibitor in 50% of patients with acquired hemophilia[52]. Other immunosuppressives should be considered if there is no response to steroids. Addition of cyclophosphamide (2.0–3.0 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, plasma exchange or infusion of IVIg.

ANTICOAGULANT THERAPY DURING PREGNANCY AND THE PERIPARTUM PERIOD

Anticoagulant therapy is indicated during pregnancy in the following cases:

(1) Prevention and treatment of venous thromboembolism (VTE);

(2) Prevention and treatment of systemic embolism in patients with mechanical heart valve prostheses;

(3) Prevention of pregnancy complications in women with antiphospholipid syndrome (APS) or other thrombophilia and prior pregnancy complications.

The anticoagulants currently available for the prevention and treatment of VTE and arterial thromboembolism include heparin and heparin-like compounds (unfractionated heparin (UFH), low-molecular weight heparin (LMWH), and heparinoids) and coumarin derivatives, e.g. warfarin. The 'direct' thrombin inhibitors, such as hirudin, cross the placenta and have therefore not yet been evaluated during pregnancy[53].

Heparins are the anticoagulant of choice during pregnancy for situations in which their efficacy is established. Neither UFH, LMWH nor heparinoids cross the placenta[54]. 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 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' gestation[55]. The risk of warfarin embryopathy is dose-dependent, with an increased risk when the daily warfarin dose exceeds 5 mg[56]. 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. Because of

the hemorrhagic risk to both mother and fetus, warfarin should be avoided beyond 36 weeks gestation.

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 < 1.5 and should be stopped at the second stage of labor or earlier if it appears that a Cesarean section may be required. In the latter case, protamine sulfate may be needed for reversal of UFH if the APTT ratio remains > 1.5. Postpartum, the heparin infusion can be restarted 4 h post-delivery 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 $> 80 \times 10^9$/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. In practice, it is reasonable to allow at least 12 h to elapse after a prophylactic dose of LMWH before inserting an epidural or spinal catheter, but a delay up to 24 h may be necessary in patients on therapeutic doses of LMWH. At least 2 h should elapse after insertion of the catheter before LMWH is given again. If there have been difficulties with the procedure, then it is prudent to delay prior to giving further prophylaxis.

Pregnant women with prosthetic heart valves pose a problem because of the lack of reliable data regarding the efficacy and safety of antithrombotic therapy during pregnancy. However, it appears reasonable to adopt one of the following three approaches:

(1) Oral anticoagulants throughout pregnancy;

(2) Replacing oral anticoagulants with UFH from weeks 6 to 12;

(3) UFH throughout pregnancy.

In the first two regimens, heparin is usually substituted for the oral anticoagulant close to term. The use of LMWH for anticoagulation in patients with artificial heart valves is still debatable.

As Walker[57] has so succinctly stated, 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 far as possible on the relative risks of the various thromboprophylaxis regimens and on whether the patient is perceived to be at higher or lower thromboembolic risk.

Women with the older type of mechanical prostheses (e.g. Starr-Edwards or Bjork-Shiley), women with a prosthesis in the mitral position, women with multiple prosthetic valves and women with atrial fibrillation may be regarded as being at high thromboembolic risk. Women with newer and less thrombogenic valves (e.g. St Jude's or Duromedics), particularly if they are in the aortic position and providing they are in normal sinus rhythm, may be regarded as being at lower thromboembolic risk.

With the information currently available, it would be prudent to advise women in the high-thromboembolic-risk category to use an oral anticoagulant with an INR target of 3.5 throughout pregnancy, although some may choose to substitute adjusted doses of heparin between 6 and 12 weeks' gestation. Warfarin should be avoided close to term and UFH or LMWH substituted. However, if labor commences in a woman on warfarin, intravenous vitamin K or fresh frozen plasma can be used to reverse its effect.

On the basis of one report that the risk of fetal complications with warfarin appears to be dose-related[56], women with mechanical heart

valves in the lower thromboembolic risk category 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 weeks 6 to 12 if their daily warfarin requirement does not exceed 5 mg. Women in this category requiring higher daily doses of warfarin may wish to minimize the risk of fetal complication, and be prepared to rely on adjusted doses of UFH and LMWH, but they must be made aware that there is less good evidence to support the use of these latter regimens. In general, women with bioprosthetic valves do not require anticoagulation, but anticoagulation may be necessary for other indications.

Clear recommendations for heparin use during labor and delivery in women with artificial heart valves are not available. Intravenous UFH at therapeutic doses may be administered until 6 h before delivery. If the UFH is to be reversed, it is usually sufficient to stop the infusion (as the half-life of the UFH is approximately 1 h). If more rapid reversal is necessary, protamine sulfate is used. One mg of protamine sulfate neutralizes 100 IU of heparin if the latter has been given within the previous 30 min. Protamine sulfate should be given slowly at 5 mg/min, with a maximum single dose of 50 mg. Protamine sulfate is much less effective in reversal of LMWH.

Warfarin is initiated in the postpartum period in patients with mechanical valves. Anticoagulation with intravenous UFH while awaiting therapeutic levels of warfarin is probably not warranted. The risk of bleeding, particularly after Cesarean section, exceeds the risk of thrombotic complications[58]. Subcutaneous UFH in prophylactic doses (5000–7500 units twice daily) may be given.

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.

Eleven cases of Bernard–Soulier syndrome in pregnant women have been described to date[59]. Most have been diagnosed prior to pregnancy, and postpartum hemorrhage has been more common than antepartum bleeding[60]. Management of bleeding in Bernard–Soulier syndrome in pregnancy is debatable; single-donor platelet transfusions (preferably HLA-matched), desmopressin (DDAVP) and antifibrinolytic agents have been successfully used[60].

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. Patients with this condition are at increased risk of primary postpartum hemorrhage. Single-donor platelets (again, HLA-matched if possible) and recombinant activated FVII have been used to control bleeding during the peripartum and the postpartum period[61].

The May-Hegglin anomaly is a rare autosomal dominant condition with thrombocytopenia and giant platelets. Platelet count varies between 40 and 80×10^9/l, but platelet function appears normal. Excess hemorrhage is uncommon, but patients may need a platelet transfusion to achieve hemostasis at delivery[62].

von Willebrand disease

von Willebrand disease (vWD) is the most common of the inherited bleeding disorders, 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 released into the plasma, and is also stored in Weibel–Palade bodies in the endothelial cells. 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 six categories (Table 6), which correspond to distinct pathophysiological 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 show 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

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 multimers, high-molecular weight multimers
Adapted from Sadler JE. *Thromb Haemost* 1994;71:520–5

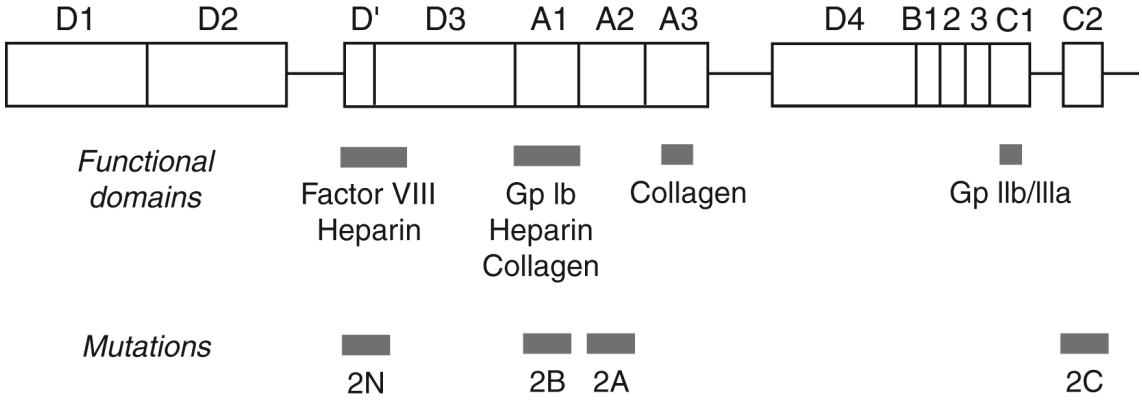

Figure 1 The von Willebrand factor. The protein consists of a series of domains with different binding sites for factor VIII, heparin, collagen and platelet glycoprotein (Gp) Ib and IIb/IIIa. The sites of gene mutations giving rise to different subtypes of VWD are marked. From Green D, Ludlam CA. VWD in bleeding disorders. *Health Press* 2004, pp. 63–69

(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 vWF[63]. 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 levels and FVIII levels, and diagnosis may be difficult in these circumstances[64]. 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 A[64].

The aim of therapy for vWD is to correct the 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 products[65].

DDAVP, a synthetic vasopressin analogue, releases vWF from endothelial stores; there is also an increase in the 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[66] and after delivery. It is effective in securing in many situations in type 1 vWD with a 3–5-fold increase in the plasma vWF and FVIII levels. It is of no therapeutic benefit in type 3 vWD because of the very low basal levels of vWF and FVIII. The response in types 2 is less predictable. DDAVP is contraindicated in patients with type 2B because it may exacerbate the coexisting thrombocytopenia. Patients should have a test of DDAVP (if possible when not pregnant) to see if it is effective in their individual case.

Plasma-derived vWF 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) > 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)[67]. vWF starts to rise as early as the 6th week and by the third trimester may have increased three- to fourfold. 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 pregnancy[68].

After delivery, FVIII and vWF in normal women fall slowly to baseline levels over a period of 4–6 weeks. However, the postpartum decline of these factors may be rapid and significant in women with vWD[68]. As the individual hemostatic response to pregnancy is variable, vWF and FVIII levels should be monitored during pregnancy and 3–4 weeks after delivery.

Antepartum hemorrhage is uncommon in women with vWD, but may occur after spontaneous miscarriage or elective termination, occasionally as the initial presentation of vWD. Women with vWD are at substantial risk for secondary postpartum hemorrhage, especially 3–5 days after delivery. vWD may also exacerbate bleeding due to other obstetric causes, such

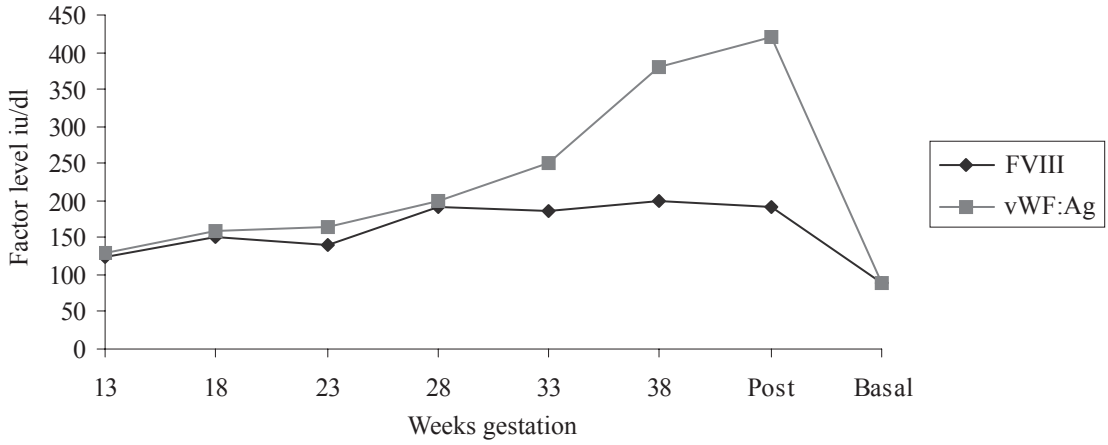

Figure 2 Levels of factor VIII and vWF in normal pregnancy. From Giangrande PL. Management of pregnancy in carriers of haemophilia. *Haemophilia* 1998;4:779–84

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. Regional analgesia may proceed in these patients after discussion with an obstetric anesthetist. Although neonatal bleeding is rare, ventouse delivery and high-cavity forceps should be avoided. Careful and prompt repair of episiotomy wounds or perineal tears is advisable.

For patients whose vWF activity (vWF:RCo) has not normalized, decisions about regional analgesia should be individualized[69]. Hemostatic supportive therapy with DDAVP or vWF concentrate should be given to cover delivery or Cesarean section if the FVIII level is less than 50% or if vWF:RCo has not normalized[66]. Because of the high incidence of secondary postpartum hemorrhage in patients with vWD, efforts should be made to ensure that placenta is complete upon expulsion or removal.

After delivery, all patients should be closely observed for postpartum hemorrhage and uncorrected hemostatic defects treated. In responsive patients, DDAVP is the treatment of choice to prevent and treat mild to moderate postpartum bleeding[70]. FVIII and vWF:RCo should be checked a few days postpartum because they may fall rapidly after delivery. FVIII and vWF:RCo should be maintained in the normal range for at least 3–7 days after Cesarean section. It is difficult and unnecessary to diagnose vWD in the neonate, except when type 3 vWD is suspected. Generally, diagnosis can be postponed until later in childhood.

HEMOPHILIAS

Hemophilias A and B are the most common severe congenital bleeding disorders associated with reduced or absent coagulation FVIII and FIX, respectively. The incidence of hemophilia A is around 1 in 10 000 live male births. Hemophilia B is about five times less common than hemophilia A. 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 have an identical presentation and 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 pedigree[71]. 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 hemophiliac 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 may be a sporadic carrier[71]. Female carriers of hemophilia may have reduced FVIII/IX levels because of random inactivation of the X-chromosome (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 and vWF rise during normal pregnancy (Figure 2). The increase is particularly marked during the third trimester, when levels of FVIII may rise to double that of 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 pregnancy in carriers of hemophilia A. 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 consent[72]. 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 carrriership if molecular diagnosis is not possible. However, normal levels of FVIII/FIX do not exclude carriership[72]. 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 intravenous DDAVP can be attempted, with measurement of the response in FVIII levels over the next 24 h.

Once carriership has been established, women should be offered prepregnancy counseling to provide them with the information necessary to make informed reproductive choices. A new technique of 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. 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 Fertilization and Embryology Authority.

If prenatal diagnosis is requested, testing is usually carried out by chorionic villus sampling (CVS) at 11–12 weeks' gestation; 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 carry out. The main adverse event related to CVS is miscarriage, which is estimated at about 1–2%. Fetal cells are karyotyped so that the fetal sex is established. If the fetus is female, no further tests are done. If the fetus is male, additional tests are conducted to establish whether the affected gene has been inherited. Cells for karyotyping and 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%. Fetoscopy to allow for fetal blood sampling is rarely performed; it can only be performed after about 16 weeks' gestation and has a substantial risk of fetal death (1–6%). 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 hemophilia[67]. When prenatal diagnosis has not been carried out but there is a risk that the child may have hemophilia, fetal sex should be diagnosed by ultrasonography[67]. This information is necessary for the obstetrician even if the parents do not wish to know the sex of the infant.

Factor VIII/IX levels in female carriers of hemophilia should be monitored regularly in pregnancy. It is particularly important to measure coagulation factor levels toward the end of the third trimester (34–36 weeks) to plan management of delivery[67]. If maternal FVIII/FIX levels remain low at 34–36 weeks in hemophilia carriers, treatment is necessary for delivery[67]. A FVIII/FIX plasma level of 40% is safe for vaginal delivery, and a level of 50% or greater is safe for Cesarean section. Epidural anesthesia may be used if coagulation defects have been corrected[67]. 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 not be used. Infection of the fetus with parvovirus may result in hydrops fetalis and fetal death.

If the fetus is a known hemophiliac, is male and of unknown hemophilia status, or is of unknown sex, care should be taken to avoid traumatic vaginal delivery. Routine Cesarean delivery is unnecessary[67], but should be carried out if obstetric complications are anticipated.

Most bleeding problems in carriers of hemophilia occur postpartum. Replacement therapy should be given immediately after delivery to mothers with 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 3–4 days after vaginal delivery and for 5–10 days after Cesarean section[73].

In the infant, intramuscular injections should be avoided until hemophilia has been excluded. Cord blood should be obtained for FVIII/FIX assays[74]. Routine administration of coagulation factor concentrates to neonates with hemophilia is unnecessary if delivery has been atraumatic and there are no clinical signs of hemorrhage[74].

RARE COAGULATION DISORDERS

Fibrinogen deficiency

The hypo- and dysfibrinogenemias comprise a collection of disorders that are usually dominantly inherited and associated with both bleeding and venous thrombotic manifestations. Women are at risk of recurrent miscarriage, and both antenatal and postnatal hemorrhage. In hypofibrinogenemia, both antigenic and functional fibrinogen levels are reduced. The diagnosis of dysfibrinogenemia is made by demonstrating a prolonged TT with a normal antigenic fibrinogen level.

Prophylaxis with fibrinogen concentrates improves pregnancy outcome and prevents antepartum and postpartum hemorrhage in women with hypo- and dysfibrinogenemia. Cryoprecipitate is a good source of fibrinogen but should not usually be used, as it is not virally inactivated. Its use may be considered in an emergency situation if no other alternatives are available. The half-life of infused fibrinogen is 3–5 days, and treatment is unlikely to be needed more often than on alternate days. Levels above 1.5 g/l are required toward the end of pregnancy and at the time of delivery[75].

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 there are consanguineous marriages. 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 10–15%[76]. 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.

The FVII level may increase up to four-fold during normal pregnancy[76]. However, it is unknown whether FVII levels increase to the same degree in pregnant women with congenital FVII deficiency as they do in normal pregnancy[77]. FVII deficiency during pregnancy is a risk factor for postpartum hemorrhage. Bleeding may occur from the placental implantation site, episiotomies, lacerations to the birth canal, or surgical trauma occurring with Cesarean delivery[78].

Recombinant activated FVII (rFVIIa) has been approved in the European Union for use in congenital FVII deficiency[79]. In places where this product is not available, fresh frozen plasma, prothrombin complex concentrates (PCCs) or plasma-derived FVII concentrate may be used. Because the patient may potentially need a Cesarean delivery and because perineal trauma cannot be anticipated, prophylaxis is usually recommended at the time of delivery[78]. Recombinant FVIIa has been given as an initial bolus injection of 20–50 μg/kg, followed by further boluses of 10–35 μg/kg every 4–6 hours to cover vaginal delivery or Cesarean section in patients with congenital FVII deficiency[78,80]. It has also been used as an initial bolus injection of 13 μg/kg with subsequent continuous infusion at 1.7–3.3 μg/kg/h for 4 days[76] (see Chapter 26).

Factor X deficiency

Congenital FX deficiency is an autosomal recessive disorder. The prevalence of the severe (homozygous) form is 1 : 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.

Thirteen pregnancies in eight patients with isolated FX deficiency have been reported in the literature[81]. The complications described include spontaneous abortions, placental abruptions, premature births and postpartum hemorrhage. 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 therapy[75]. 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 hemostasis[75] and are required at the time of delivery.

FX is present in intermediate-purity FIX concentrates (prothrombin complex concentrates, PCCs). FX levels should be monitored as caution is required because of the prothrombotic properties of these concentrates. Fresh frozen plasma may be an alternative when prothrombin complex concentrates are not available.

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 < 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, prothrombin complex concentrates 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 plasma[82].

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 : 1 000 000 but partial deficiency is much more common. FXI deficiency is unlike most of the other rare coagulation disorders in that heterozygotes may have a significant bleeding tendency that is poorly predicted by the FXI level. 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. FXI deficiency rarely results in bleeding during pregnancy, but women with severe or partial deficiency may suffer postpartum bleeding[75].

The APTT is usually prolonged and diagnosis is confirmed by finding a low FXI level. The deficiency is classified as severe if the FXI level is less than 15% and partial at 15–70%; the lower limit of the normal range is 70%. There is controversy about changes in FXI levels during normal pregnancy, some studies demonstrating an increase and others a decrease[83]. Changes in FXI levels in women with FXI deficiency have been inconsistent during pregnancy[84]. It is therefore recommended that FXI levels should be checked at the initial visit, and during the third trimester in FXI-deficient women.

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 postpartum hemorrhage which is a common presentation of FXI-deficient patients[84]. 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 > 50% 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%[84]. Concurrent use of tranexamic acid or other antifibrinolytic drugs with FXI concentrate should be avoided. Fresh frozen plasma 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 overload[75]. Recombinant FVIIa has been used successfully to manage adult patients with FXI deficiency undergoing surgery, although it is not licensed for this indication[75].

Factor XIII deficiency

Congenital FXIII (fibrin stabilizing factor) deficiency is an autosomal recessive disorder. It 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. Spontaneous abortions occur in early pregnancy because FXIII is required for successful implantation. Women with FXIII deficiency are also at increased risk of postnatal bleeding[75]. 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.

FXIII has a half-life of 7–10 days and therefore only needs to be given at 4–6-weekly intervals to maintain a level > 3% which is necessary to prevent spontaneous intracranial bleeds. Up to 50% of severely (FXIII level < 1%) affected women may miscarry without appropriate FXIII treatment[75]. All severely affected individuals should be started on monthly infusions of plasma--derived FXIII concentrate from the time of diagnosis to prevent intracranial bleeds and these should be continued during pregnancy[75]. FXIII levels fall throughout pregnancy and should be monitored, aiming to keep the trough level > 3%.

FXIII deficiency may also cause life-threatening hemorrhage in the neonate with levels < 3%. The disorder can be diagnosed from cord or peripheral blood samples. Treatment of an acute bleeding episode is with FXIII concentrate at a dose of 20 IU/kg[75].

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