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ESSENTIALS Plasma volume increases by more during pregnancy than does red cell mass, leading to haemodilution and a fall in the haematocrit from about 40% to 33%, with a nadir usually reached at 24–32 weeks' gestation. Anaemia during pregnancy is defined as a haemoglobin concentration of below 105 g/litre during the second and third tri- mesters and below 110 g/litre in the first trimester. Anaemias and haemoglobinopathies The commonest haematological problem encountered in preg- nancy is iron-deficiency anaemia. Routine iron supplementation in all pregnant women is probably not justified in developed countries, but if iron deficiency is detected it is advisable to treat as early as possible. Folic acid—the requirement for folic acid doubles in pregnancy and dietary folate deficiency is the most frequent cause of gestational megaloblastic anaemia. This can be prevented by supplementation with 300 µg folic acid daily, although higher doses of folate (up to 5 mg daily) are recommended to prevent neural tube defects. Haemoglobinopathies—the diagnosis of variant haemoglobins and the thalassaemia syndromes before pregnancy or early in ges- tation is important. Screening is usually performed on a blood sample taken at booking. If a haemoglobin variant or thalassaemic indices are detected, then the partner should be tested to determine the risk of having an affected fetus and allowing informed prenatal counselling. Haemostatic disorders Normal pregnancy is associated with marked changes in all aspects of haemostasis, the overall effect of which is to generate a state of hypercoagulability. These changes in haemostasis, while reducing the risks of excessive blood loss at delivery, significantly increase the risk of venous thromboembolic disease in pregnancy. Gestational thrombocytopenia—seen in about 8% of all preg- nancies and accounts for more than 70% of cases of thrombo- cytopenia in pregnancy: its main differential diagnosis is immune thrombocytopenic purpura. Disseminated intravascular coagulation—can be caused by intra- uterine death with a retained fetus, severe pre-eclampsia, pre- mature separation of the placenta (placental abruption), retained placenta, amniotic fluid embolism, haemorrhagic shock, and trans- fusion reaction. Inherited haemostatic disorders (e.g. haemophilia, von Willebrand disease)—women with these conditions require specialist manage- ment during pregnancy. Anaemia Physiology Hormonal changes in pregnancy can significantly alter haemato- logical parameters. An understanding of these changes can avoid misinterpreting them as abnormal.

During pregnancy the total blood volume will increase by about 1.5 litres. This is mainly due to an expansion of the plasma volume by 25–80%. This increase occurs mainly after the first trimester and peaks at 34–36 weeks' gestation. The increase is greater in multip- arous women with larger babies and in multiple pregnancies. The red cell mass also increases by 10–20%, again after the first trimester. This can increase further in women taking iron supplementation. The consequence of the greater relative increase in the plasma volume leads to haemodilution and a fall in the haemoglobin by 10–20 g/litre. The nadir is usually reached at 24–32 weeks' gestation, with the haemoglobin then starting to rise again towards term. The degree of haemodilution shows considerable variation between women, which means that haemoglobin alone is not a valid marker of iron status. The World Health Organization (WHO) defines anaemia in pregnancy as a haemoglobin below 110 g/litre at any time during pregnancy and below 100 g/litre following delivery. There is, how- ever, significant variation in haemoglobin levels and in the United Kingdom a level of 110 g/litre or greater appears adequate in the first trimester and 105 g/litre or greater in the second and third trimesters. During pregnancy the mean cell volume will increase by about 5–10 fl in iron replete women, independent of the vitamin B12 and folate levels. There is also a gradual increase in erythropoietin levels with increasing gestation. In pregnancy it is unusual to have haemoglobin levels of more than 135 g/litre. When this does occur, it may be due to inadequate plasma volume expansion and can be associated with pregnancy- related problems (e.g. pre-eclampsia, poor fetal growth). 14.17 Blood disorders in pregnancy David J. Perry and Katharine Lowndes

Section 14 Medical disorders in pregnancy 2688 Iron-deficiency anaemia During pregnancy the daily requirements for iron increase from 0.8 to 7.5 mg/day between the first and third trimesters. Iron is needed to expand the maternal red cell mass, fulfil fetal requirements, and to prepare the mother for blood loss at delivery. There is also an in- creased iron requirement during lactation. This increased require- ment is met by increased absorption, which is most pronounced after 20 weeks' gestation. Iron-deficiency anaemia is the commonest haematological problem encountered in pregnancy. Worldwide it affects about 20% of women and is a significant cause of morbidity and mor- tality. In nonpregnant individuals iron deficiency frequently mani- fests as a hypochromic, microcytic anaemia, but in the pregnant woman, owing to a relative increase in the number of larger im- mature red cells, the mean cell volume may remain unchanged. The red cell distribution width, however, increases. A serum fer- ritin below 30 µg/l reflects a loss of storage iron and indicates iron deficiency, and this occurs before the haemoglobin falls, which is a relatively late manifestation. Mothers that enter pregnancy iron deficient will have no stores remaining at term, and it takes about two years of normal dietary iron to replace the iron lost with each pregnancy. The level of transferrin, the iron binding protein in plasma, doubles during the course of pregnancy leading to a fall in per- centage transferrin saturation. Transferrin receptors are present on the surface of young erythrocytes and also circulate within the blood as soluble transferrin receptors (sTfR). These increase in number during iron deficiency and are independent of total body iron stores. They can, therefore, be a helpful measure of iron defi- ciency in women with a raised ferritin for other reasons. Mild iron-deficiency anaemia is unlikely to have any harmful ef- fects on the mother, although it has been associated with irritability and poor concentration. Severe iron deficiency is associated with pallor, glossitis, angular chelitis, and koilonychia. The symptoms of anaemia can make the last few weeks of pregnancy difficult to tol- erate. Women that are iron deficient are unlikely to tolerate signifi- cant blood loss at delivery and may, in fact, have increased blood loss due to impaired neuromuscular transmission. An uncorrected an- aemia may be

associated with placental enlargement, which in turn leads to a higher incidence of fetal abnormalities, low birth weight, and increased preterm births. Iron deficiency can also affect cellular immunity and phagocytosis making those affected more susceptible to infection. Iron replacement Routine iron supplementation in all pregnant women is probably not justified in developed countries. However, if iron deficiency is detected it is advisable to treat as early as possible as the demands for iron will increase as the pregnancy progresses. The recom- mended dose of oral elemental iron is 100–200 mg daily. Once the haemoglobin has reached the normal range the supplementation should be continued for three months to replenish iron stores. Side effects are experienced by 10–20% of patients due to nausea, ab- dominal discomfort, and altered bowel habit. In these situations, liquid preparations that have lower iron doses can be given and then titrated up according to symptoms. Alternatively, the iron can be given parenterally, although most parenteral iron preparations are relatively contraindicated in the first trimester of pregnancy. A maximal increase in haemoglobin of approximately 0.8 g/week can be expected. Pregnancy can have a profound effect on a woman’s iron stores, with nulliparous women having higher serum ferritin levels than multiparous women. These differences can persist even into meno- pause. However, if iron supplementation is given, the haemoglobin will reach pre-pregnancy levels within five to seven days of delivery assuming there has not been excessive blood loss. Vitamin B12 and folate deficiency Vitamin B12 and folate are required in pregnancy for the growing uterus, fetus, and the expanding red cell mass. The requirement for folic acid doubles in pregnancy and dietary folate deficiency is the most frequent cause of gestational megaloblastic anaemia. Megaloblastic anaemia secondary to a deficiency of either vitamin B12 and/or folate is most common in those countries with inad- equate nutrition. Folate deficiency is more frequent in multiple preg- nancies and multiparous women, with most cases presenting in the third trimester and post-partum. Folate deficiency is known to be associated with an increase in neural tube defects but can also lead to an increased incidence of prematurity and low birth weight infants. In most women the diagnosis of folate deficiency is made in the last four weeks of pregnancy, usually as a failure to respond to iron supplementation. Few symptoms may be present. An earlier presen- tation in the second trimester should prompt a search for another cause of folate deficiency such as chronic haemolysis, malabsorption, or anticonvulsant therapy. Folate supplementation is recommended prior to conception and during the first trimester to prevent neural tube defects. The current recommendation is 400 µg daily which will reduce the risk of neural tube defects by 36%, but there is a linear dose response, and a dose of 5 mg daily improves this reduction to 85%. Megaloblastic anaemia due to poor dietary folate intake is prevented by 300 µg daily, but if the folate deficiency is due to malabsorption it will need to be given parenterally. Initial concerns that folate supplementation would mask an underlying B12 deficiency, allowing continued neurological deteri- oration, have not been borne out. This is probably because severe B12 deficiency due to Addisonian pernicious anaemia and of sufficient severity to cause megaloblastosis is likely to be associated with in- fertility. Vitamin B12 stores are large (about 3000 µg) and therefore more or less unaffected by pregnancy. The daily requirements for vitamin B12 are increased in pregnancy (1.4 µg/day in pregnancy vs. 1.0 µg/day in the nonpregnant female) but this is easily met by a diet containing animal products. Dietary deficiency of vitamin B12 is rare in pregnancy, but can occur and was previously termed the ‘perni- cious anaemia of pregnancy’. However, it responds to oral vitamin B12 supplementation and is not associated with an autoimmune aeti- ology. The exception is those patients that have had bariatric sur- gery or a partial gastrectomy and are therefore deficient in intrinsic factor. These patients will require intramuscular B12 replacement. B12 levels can fall up to 50% during pregnancy, particularly in the third trimester. This is normal and

represents a dilutional effect and increasing binding to the B12 biding proteins, and it does not require replacement. The reference ranges stated are for nonpregnant individuals.

14.17 Blood disorders in pregnancy 2689 Haemoglobinopathies Genetic defects in the structure, function, and production of haemo- globin can be divided into two clinically significant groups: variant haemoglobins and the thalassaemia syndromes. Diagnosis prior to, or early in, pregnancy is important so that obstetric management can be tailored appropriately. It is also possible to offer prenatal diagnosis, which can shape parental decisions with regards to termination of the pregnancy or can direct materno-fetal management prior to delivery. Screening is usually performed on the blood sample taken at booking. This can be directed at high-risk populations; however, with the increased migration of people from varied racial back- grounds it can be difficult to isolate this population accurately, and therefore it is prudent to offer the screening to all mothers. An al- gorithm for screening blood tests is outlined in Fig. 14.17.1. If a haemoglobin variant or thalassaemic indices are detected, then the partner should be tested to determine the risk of having an affected fetus and allowing informed prenatal counselling. Variant haemoglobins and sickle cell syndromes Clinically the important haemoglobin variants are those that are as- sociated with red cell sickling. The sickle cell syndromes with major clinical symptoms include sickle cell anaemia (HbSS), sickle cell haemoglobin C (HbSC) disease, and sickle cell β-thalassaemia (HbS β-Thal). Other haemoglobin variants in combination with HbS (e.g. HbSE and HbSD are in general associated with a milder disorder, but vasocclusive crises may occur in pregnancy). Mothers with sickle cell trait (i.e. heterozygotes for haemoglobin A and S; HbAS) have no increased risk of sickle cell crises during normal pregnancy, but they do have an increased incidence of some infections (e.g. pyelonephritis). Caution should also be exercised if a general anaesthetic is required in these women as they have an in- creased risk of placental infarction and pre-eclampsia if exposed to severe dehydration or shock. Outcome data in pregnancy for women with sickle cell disease (i.e. HbSS, HbSC and HbS β-thal), is based upon retrospective case series; overall maternal mortality is below 2% and neonatal mor- tality is below 5%. There is an increased tendency to pre-eclampsia, preterm labour, and low birth weight babies. The main medical problems facing a pregnant woman with sickle cell disease are those of increased sickle cell crises causing tissue infarction, severe an- aemia, and an increased risk of infection. The crises are predomin- antly vaso-occlusive in nature and can be triggered by infection, or the pregnancy alone. If this is associated with a parvovirus infec- tion, then the crisis can become aplastic resulting in a rapid drop in haemoglobin. Painful vaso-occlusive crises can occur in any organ leading to infarction and dysfunction, however the lungs are par- ticularly susceptible and can progress to a life-threatening chest crisis. Treatment of a sickle crisis in pregnancy is the same as for the non-pregnant female; namely oxygen, fluids, and analgesia with the add- ition of antibiotics if an infective trigger is suspected. There should be a low threshold for proceeding to red cell exchange transfusion if the mother is not improving. It is particularly important that preg- nant women with sickle cell disease are on continuous folic acid supplementation due to the high erythrocyte turnover rate. Also, as most adults with sickle cell disease have functional hyposplenism, they should receive pneumococcal vaccination and twice daily peni- cillin prophylaxis. In the sickle cell syndromes, no correlation has been shown be- tween the degree of anaemia and obstetric or perinatal complica- tions. In addition, no benefit has been shown by prophylactic red cell transfusion to keep the haemoglobin at 100–110 g/litre, rather than transfusing when indications arise. In addition to the issues of cost and availability, prophylactic transfusion exposes the mother to the hazards of blood transfusion including infection and not- ably the risk of alloimmunization of

the mother to minor red blood cell antigens. This can lead to severe, delayed, and sometimes fatal haemolytic reactions in the mother and haemolytic disease of the fetus and newborn. Indications for transfusion in sickle cell disease women during pregnancy are: anaemia associated with cardiac or respiratory compromise, severe sickle cell disease-related complica- tions (e.g. acute chest syndrome); preparation for caesarean section or refractory pre-eclampsia in previous pregnancies. More contro- versial indications are: increasing frequency of painful crises; sickle cell disease-related complications during a previous pregnancy; and multiple gestation pregnancy. The increased risk of intrauterine growth restriction is probably due to the decreased oxygen supply from the maternal anaemia and some placental infarction. Fetal growth should therefore be moni- tored with regular ultrasound scans. The method of delivery is based on obstetric considerations. For the infant, the first two years of life are particularly hazardous with an increased risk of death due to in- fection and splenic sequestration. Therefore, if the diagnosis is not made antenatally, then it needs to be made as soon as possible after birth so that the parents can be aware of the need to investigate and treat any new symptoms early. Most pregnancies have a successful outcome, but early collabor- ation between obstetric and haematology teams is strongly recom- mended if there are any concerns. Thalassaemias Alpha(α) Thalassaemia There are four clinical syndromes dependent on the number of α- genes that have been deleted.

1. Four gene deletion α-thalassaemia (--/--) (i.e. a complete ab- sence of all four α-globin genes), results in a fetus that cannot make any α-chains and therefore no fetal or adult haemoglobin can be synthesized. The remaining γ-chains form tetramers known as haemoglobin Barts (Hb Barts—γ4). Hb Barts has a high oxygen affinity, which restricts oxygen delivery to the tissues resulting in a hydropic fetus that usually dies in utero or shortly after birth. Pregnancy with an α-thalassaemia hydrops fetus is associated with severe hypertension and proteinuria early in pregnancy, along with a high risk of antepartum and post-partum haemorrhage in addition to other obstetric complications secondary to a large fetus and bulky placenta. Routine antenatal screening can detect women at risk of carrying an affected fetus. Parents should be referred for counselling and offered prenatal diagnosis as termination of the pregnancy may be required to avoid serious obstetric complications. Most cases of Hb Barts hydrops fetalis are seen in the Far East. However, with migra- tion, this disorder will become more prevalent in Western countries.

Section 14 Medical disorders in pregnancy 2690 Transfusion in utero has been performed and has been successful in a few cases. 2) Haemoglobin H (--/-α) is the result of the deletion of three α-globin genes. The fetus can, therefore, make some α-chains, so although most of the haemoglobin will be Hb Barts there will be some fetal Hb (HbF (α2γ2)) production. The neonate appears healthy at birth but soon develops a severe haemolytic anaemia as HbF levels fall. The Hb Barts (γ4) is replaced with HbH (β4), which FBC Raised HbF Normal: iron deficiency; α thal trait; normal A2 - β thal trait Raised: β thal trait Borderline: β thal trait,

- α thal trait, β thal trait + Fe def. mild β thal trait, normal Hb electrophoresis or equivalent test Variant haemoglobin present HbA2 quantification Confirmatory tests Test partner, retest patient Test partner Test partner No further action Quantitate HbA2 in partner and arrange DNA analysis of both patient and partner No further action Partner has elevated HbA2 Patient is Mediterranean, Saudi Arabian, or South Asian Risk of normal A2 - β thal

trait or coexisting β and δ thal trait: do red cell indices and Hb Electrophoresis on partner and if MCH <27 pg measure HbA2 Patient is Chinese, South East Asian, Greek, Turkish, or Cypriot and has MCH <25 pg Partner has elevated normal HbA2 Partner has normal Hb Electrophoresis and indices Arrange DNA analysis of patient and partner If patient and partner consanguinous arrange DNA analysis of both; if not then no further action Partner is also of one of the above ethnic groups and has MCH <25pg Risk of α° thal trait: do red cell indices on partner Consider red cell indices and test partner δ β thal trait or HPFH Hb S,C,E,D-Punjab, O-Arab, Lepore Patient is Northern European, African, or Afrocaribbean Partner abnormal, patient borderline Reconsider MCH and ethnic origin MCH <27pg. any ethnic group Quantitate, if >5% do Kleihauer test MCH ≥27pg. any ethnic group or any ethnic group except Northern European* Confirm diagnosis in partner: test DNA of patient for α and β thal trait including normal A2 - β thal trait Fig. 14.17.1 An algorithm for screening for haemoglobinopathies in pregnant women.

14.17 Blood disorders in pregnancy 2691 results in a lifelong anaemia. This varies in severity and will worsen during pregnancy. 3) Mothers with one (-α/αα) or two gene deletion α-thalassaemia (--/αα or -α/-α) can range from being asymptomatic to having a mild hypochromic microcytic anaemia. In all women with sus- pected two gene deletion α-thalassaemia, their partner should be screened and if necessary they should be referred for gen- etic counselling. Two gene deletion α-thalassaemia does not affect the pregnancy, but if both parents possess two gene deletion α-thalassaemia and the deletion occurs on the same al- lele (i.e. --/αα) then there is a 1:4 chance of having a Hb Barts hydropic fetus. β-Thalassaemia The β-thalassaemias are due to point mutations in the β-globin genes that cause varying degrees of reduction in the amount of β- chains produced.

1. In β-thalassaemia major, the production of β-globin chains is severely impaired, because both β-globin genes are mutated. The severe imbalance of globin chain synthesis results in ineffective erythropoiesis and a severe microcytic hypochromic anaemia. The excess unpaired α-globin chains aggregate to form precipitates that damage red cell membranes, resulting in intravascular haem- olysis. Premature destruction of erythroid precursors results in intramedullary death and ineffective erythropoiesis. This is not ap- parent in the fetus until the HbF production switches to HbA when the infant will become anaemic. Women with transfusion-dependent β-thalassaemia major have historically been infertile however with improving iron chelation the number of successful pregnancies is increasing. There are also an increasing number of women with thalassaemia intermedia pro- ceeding to pregnancy. Both groups of women have an increased incidence of antepartum and post-partum complications with intra- uterine growth restriction, recurrent infections, and hypersplenism. They need to continue with regular transfusions throughout preg- nancy with the incumbent risks and complications. Iron chelation therapy is not recommended in pregnancy, therefore consideration should be given to aggressive preconception chelation therapy.
2. In β-thalassaemia minor (β-thalassaemia trait), one of the two β-globin genes is defective. The defect can be a complete ab- sence of the β-globin protein or a reduced synthesis of the β-globin protein. Women with β-thalassaemia minor are either asymp- tomatic or have a mild hypochromic microcytic anaemia with a raised proportion of HbA2 which does not affect the pregnancy. However, it is important to identify such women and screen their partners to see if they are similarly affected and if necessary to offer prenatal diagnosis.

In cases in which both partners have β-thalassaemia minor, there is a 1:4 chance of having a child with severe β-thalassaemia major. Other anaemias Aplastic anaemia Coincidental aplastic anaemia can occur in pregnancy in the same way as acute leukaemia, however, there does appear to be a rare form of aplasia that develops due to the hormonal influences of pregnancy and may resolve following delivery. Diagnosis is often made in the second and third trimesters, and treatment depends on the severity of the aplasia. Haemolytic anaemia Pregnancy-related autoimmune haemolytic anaemia is a rare dis- order, but pregnancy can act as a trigger. Secondary causes include lymphoproliferative disorders, connective tissue disorders, and infections. If triggered by pregnancy it usually occurs in the third trimester and remits spontaneously following delivery. Treatment aims to maintain the haemoglobin at an adequate level for placental perfusion and minimal symptomatic anaemia. Corticosteroids and intravenous immunoglobulin are often used but may not always be effective. Red cell transfusions may be required. Disorders of haemostasis in pregnancy Physiology Normal pregnancy is associated with marked changes in all aspects of haemostasis the overall effect of which is to generate a state of hypercoagulability (Table 14.17.1). The reason for this is clear when one considers that at the time of delivery, placental separation pro- vokes an acute massive blood loss in the region of 700 ml/minute, which must be stopped immediately. Three weeks after delivery most of the changes in clotting factors have returned to normal. Table 14.17.1 Haemostatic changes in normal pregnancy Haemostatic factor Effect of pregnancy Platelet count Decreases during pregnancy Factor XIII, V Increase in early pregnancy but returns to the pre-pregnancy state by the 3rd trimester Factors XII, X, VIII, VII, VWF, and fibrinogen Increase throughout pregnancy Factor IX No change Factor XI Either no change or a slight fall Protein C and Antithrombin No change Protein S Progressive decrease during pregnancy Activated Protein C resistance (APCr) Gradual fall during pregnancy PAI-1, TAFI Increases throughout pregnancy PAI-2 Appears during pregnancy PAI, plasminogen activator inhibitor; TAF, thrombin-activatable fibrinolysis; VWF, von Willebrand factor.

Section 14 Medical disorders in pregnancy 2692 These changes in haemostasis, while reducing the risks of exces- sive blood loss at delivery, significantly increase the risk of venous thromboembolic disease in pregnancy. Increasingly it is recognized that disordered haemostasis has a role in intrauterine growth re- striction, pre-eclampsia, early and late pregnancy loss, and placental abruption. Thrombocytopenia in pregnancy Thrombocytopenia is a common finding in pregnancy and may be due to a variety of causes (Table 14.17.2). Gestational thrombocytopenia Gestational thrombocytopenia is seen in approximately 8% of all pregnancies and accounts for more than 70% of cases of thrombo- cytopenia in pregnancy. The aetiology is unknown but probably represents increased peripheral destruction. The platelet count is, in general, only mildly reduced, and in 95% of women is between 100 and 150 × 109/litre. Rarely does the count fall below 80 × 109/litre. The major differential diagnosis is between gestational thrombo- cytopenia and immune thrombocytopenic purpura. Immune thrombocytopenic purpura Immune thrombocytopenic purpura has a prevalence of 1–5 cases per 10 000 pregnancies (i.e. approximately 100 times less common than gestational thrombocytopenia). Chronic immune thrombocytopenic purpura, characterized by immunologically me- diated platelet destruction, is two to three times more common in women than men. The diagnosis of immune thrombocytopenic purpura is largely one of exclusion as there is no confirmatory la- boratory test. In pregnancy immune thrombocytopenic purpura has

implications for both the mother and the fetus. All women with platelet counts below 100 × 109/litre should be screened for clinical or laboratory evidence of pre-eclampsia, a coagulopathy, or autoimmune disease. A screen for antinuclear anti- bodies should be performed and if positive it is essential to screen for anti-Ro and anti-La antibodies. Anti-Ro and anti-La antibodies can result in congenital heart block in approximately 2% of infants born to mothers with such antibodies. Asymptomatic women with platelet counts more than 20 × 109/ litre do not require treatment until within a few weeks of delivery but should be carefully monitored, both clinically and haematologically. Platelet counts of more than 50 × 109/litre are regarded as safe for normal vaginal delivery and for caesarean section but would pre- clude the use of spinal anaesthesia for which the platelet count should be more than 80 × 109/litre. Because of the theoretical risk of haematoma formation and neurological damage, spinal or epi- dural anaesthesia is not recommended if the platelet count is below 80 × 109/litre. Therapies aimed at increasing the platelet count during preg- nancy or prior to delivery include the use of oral prednisolone or intravenous immunoglobulin. Splenectomy is rarely performed during pregnancy. The mode of delivery for women with immune thrombocytopenic purpura is dictated by obstetric reasons rather than the platelet count. There is no good evidence that caesarean section is less traumatic than an uncomplicated vaginal delivery. The major risk to the fetus is of neonatal thrombocytopenia. The platelet count may be low at birth but reaches a nadir on day 3 following delivery. The risk of neonatal thrombocytopenia does not correlate with the maternal platelet count, although a previous splenectomy for immune thrombocytopenic purpura or a previ- ously affected infant with significant thrombocytopenia may in- crease the risk of significant fetal thrombocytopenia in subsequent pregnancies. Alloimmune thrombocytopaenia In this disorder the maternal platelet count is normal, but the mother is sensitized to paternally derived fetal platelet antigens the most common of which is HPA-1. This can result in severe fetal and neo- natal thrombocytopenia beginning early in pregnancy. Women at risk can be tested for the presence of platelet alloantibodies during gesta- tion. In neonates with severe thrombocytopenia, the most common presentations are petechiae, purpura, or cephalohaematoma at birth, associated with major risk of intracranial haemorrhage (up to 20% of reported cases), which leads to death or neurological sequelae. The treatment of affected infants involves the transfusion of compat- ible platelets and washed maternal platelets are often used. Antenatal management is controversial but can include a combination of ma- ternal intravenous γ-globulin administration, intrauterine platelet transfusions, and corticosteroid therapy, while monitoring fetal platelet counts closely throughout the pregnancy. HELLP The HELLP syndrome comprises a haemolytic anaemia, elevated liver enzymes, and a low platelet count. It occurs in 0.2–0.6% of all Table 14.17.2 Causes of thrombocytopenia in pregnancy Increased destruction or utilization • Immunologic Immune thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE) • Consumption Disseminated intravascular coagulation (DIC) • Microangiopathies

- Haemolysis, elevated liver enzymes, low platelets (HELLP)
- Thrombotic thrombocytopenic purpura (TTP)
- Haemolytic uraemic syndrome (HUS) • Gestational thrombocytopenia Decreased production Leukaemia, aplastic anaemia, folate deficiency, medications, viral infections Sequestration e.g. secondary to portal hypertension

 pregnancies and about 4–5% of pregnant women with pre-eclampsia or eclampsia. Pregnancy-induced hypertension, pre-eclampsia, and the HELLP

syndrome are related and overlap in their presentations. The syndrome is a subtype of severe pre-eclampsia and appears to be secondary to microvascular endothelial damage and intravascular platelet activation. The haemolysis in the HELLP syndrome is a microangiopathic haemolytic anaemia. Red blood cells become fragmented as they pass through small blood vessels with endothelial damage and fi- brin deposits. The elevated liver enzyme levels in the syndrome are thought to be secondary to obstruction of hepatic blood flow by fi- brin deposits in the sinusoids. The thrombocytopenia has been at- tributed to increased consumption and/or destruction of platelets. Thrombotic thrombocytopenic purpura Thrombotic thrombocytopenic purpura is a life-threatening multi system disorder characterized by a pentad comprising: • Microangiopathic haemolytic anaemia • Thrombocytopenia • Neurological abnormalities • Fever • Renal dysfunction In most cases of acquired thrombotic thrombocytopenic purpura in pregnancy, women develop an autoantibody directed against ADAMTS13 and as a consequence cannot break down the ultra large von Willebrand factor multimers that are secreted from endothelial cells. The absence of this cleavage and the presence of ultra large von Willebrand factor multimers in the circulation is believed to lead to platelet activation and the generation of platelet microthrombi. Congenital thrombotic thrombocytopenic purpura is a rare dis- order due to a mutation within the gene encoding ADAMTS13 that results in a deficiency or functional abnormality of the protein. Although congenital thrombotic thrombocytopenic purpura usu- ally presents in childhood, there are cases in which the presentation is in adulthood. The diagnosis of thrombotic thrombocytopenic purpura is a clin- ical one, although assays for ADAMTS13 are available and can be helpful in distinguishing thrombotic thrombocytopenic purpura from other disorders. The mainstay of treatment for thrombotic thrombocytopenic purpura is early plasma exchange to remove the autoantibody and to increase ADAMTS13 levels, and with the intro- duction of this treatment the survival rate has improved from ap- proximately 3% prior to the 1960s to 82%. Steroids may also be helpful in thrombotic thrombocytopenic purpura in addition to plasma exchange. Patients also have an increased risk of venous thrombo- embolic disease and are therefore maintained on low-dose aspirin. In the nonpregnant setting, there is extensive use of the anti-CD20 monoclonal antibody Rituximab. This has been used successfully in some pregnancies, but pregnancy remains a relative contraindication. Disseminated intravascular coagulation Disseminated intravascular coagulation is an acquired syndrome characterized by the intravascular activation of coagulation. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction. Disseminated intravascular coagulation is not confined to pregnancy and can arise for a variety of reasons including sepsis, major trauma, and an incompatible blood transfusion. In pregnancy, disseminated intra- vascular coagulation may occur secondary to: • Intrauterine death with a retained fetus • Severe pre-eclampsia • Premature separation of the placenta (placental abruption) • Retained placenta • Amniotic fluid embolism • Haemorrhagic shock • Transfusion reaction Systemic activation of the clotting cascade leads to depletion of pro- coagulant clotting factors, consumption of the natural anticoagu- lants that regulate the activity of clotting cascade (antithrombin, protein C, and protein S), activation of the fibrinolytic system leading to hyperfibrinolysis, and consumption of platelets leading to thrombocytopenia The main clinical manifestation of disseminated intravascular coagulation is haemorrhage secondary to the consumption of clot- ting factors and platelets. Treatment of disseminated intravascular coagulation involves identifying and removing the trigger and re- placing the missing clotting factors with fresh frozen plasma, re- storing fibrinogen with cryoprecipitate or fibrinogen concentrate, and correcting the thrombocytopenia with platelet transfusions. Inherited disorders of haemostasis Haemophilia A and B in pregnancy Haemophilia A and B are uncommon X-linked

disorders due to mutations within the genes for factor VIII (F8) and factor IX (F9), respectively. Female carriers of haemophilia A or B may have low levels of factor VIII (FVIII) or factor IX (FIX) as a consequence of Lyonization. Rarely women who are carriers may have severe haemophilia either because of extreme Lyonization or because they have a second mutation in the other F8 or F9 gene. Counselling should be offered to all potential carriers of haemo- philia to discuss prenatal diagnosis and other aspects of pregnancy management. Their carrier status should be established by DNA analysis. Women who may require blood product therapy should be immunized against hepatitis B. Initial fetal sexing is performed by cell-free fetal DNA (cffDNA) analysis of maternal plasma. This can be undertaken at seven to nine weeks of pregnancy and if it indicates a male then prenatal diag- nosis by chorionic villus sampling or amniocentesis can then be performed to allow identification of an affected male fetus. Direct mutation analysis has now almost entirely replaced the use of linkage analysis in both carrier detection and prenatal diagnosis. Factor VIII levels increase significantly during pregnancy, but this rise is unpredictable and a few women may still have low levels at the time of delivery. FVIII and FIX levels should be checked at booking, at 28 weeks, and again at 34 weeks. If the levels are low (<0.50 IU/ ml) at 34 weeks they are unlikely to rise into the normal range by delivery and treatment to prevent haemorrhage will be required. Factor IX levels do not rise during pregnancy. Women who undergo any form of invasive prenatal diagnostic procedure or who have a spontaneous abortion, or a termination of pregnancy will require prophylactic replacement therapy if their factor levels are below 0.50 IU/ml. Women who require clotting factor replacement should receive recombinant products.

Section 14 Medical disorders in pregnancy 2694 Epidural anaesthesia may be safely used in haemophilia carriers providing a coagulation screen (including the platelet count) is normal and the factor level is 0.50 IU/ml or greater. Von Willebrand disease in pregnancy Von Willebrand disease is due to a deficiency or functional abnor- mality of von Willebrand factor (VWF). Von Willebrand factor has two main functions, first as a carrier protein for factor VIII, and secondly as an adhesive protein involved in vessel wall–platelet interaction. Its function as an adhesive protein is most important in situations of high shear stress. Inherited defects in von Willebrand factor may, therefore, cause bleeding by impairing either platelet ad- hesion or fibrin clot formation. Von Willebrand disease is the most common of the inherited dis- orders of coagulation and is classified into types 1, 2, and 3. Type 1 accounts for 80% of cases and is a partial quantitative defect. Type 3 is rare and represents a complete absence of von Willebrand factor in plasma. Type 2 (subclassified into types 2A, 2B, 2M, and 2N) rep- resents qualitative defects in von Willebrand factor. In women with type 1 von Willebrand disease, the levels of von Willebrand factor increase during pregnancy and usually normalize by delivery. In type 2 von Willebrand disease, while levels may in- crease, this increase is of a functionally abnormal protein and re- placement therapy may be required at the time of delivery. In women with type 1 or 2 von Willebrand disease, von Willebrand factor levels should be checked at 34–36 weeks. Vaginal delivery is generally regarded as safe in types 1 and 3 if von Willebrand factor activity (VWF:RCo) is more than 0.50 IU/ml. Von Willebrand factor activity should be more than 0.50 IU/ml for caesarean section. In type 3, the levels will remain low and replacement therapy with a von Willebrand factor-containing concentrate will be needed at the time of delivery. In women with type 1 von Willebrand disease, von Willebrand factor levels may fall rapidly following delivery although the rate of fall is unpredictable. In some women a rapid fall in von Willebrand factor levels may lead to a delayed post-partum haemorrhage and women should be made aware of this possibility. Desmopressin is widely used in the treatment of type 1 von Willebrand disease, tended to be avoided in pregnancy because of concerns that it may cause

vasoconstriction with subsequent pla- cental insufficiency, increase the risk of premature labour due to the drug's potential oxytocic effect and increases the risk of maternal and neonatal hyponatraemia. However, desmopressin increases the levels of factor VIII and von Willebrand factor via its action on V2 receptors and its potential for vasoconstriction and uterus con- traction is negligible because the compound is practically devoid of these biologic activities related to the activation of V1 vasopressin receptors. Factor XI deficiency Factor XI deficiency is a recessively inherited disorder that is rare ex- cept in Ashkenazi Jews, where the frequency of heterozygosity may approach 10%. There is a poor correlation between absolute Factor XI levels and the risk of bleeding but individuals with levels below 0.30 IU/ml tend to have a positive bleeding history. Observations of FXI levels in pregnancy are contradictory but changes are gen- erally not clinically significant. Women with FXI levels in the het- erozygous range may bleed at delivery. In women with FXI levels between about 0.15 IU/ml and 0.70 IU/ml and no bleeding history but previous haemostatic challenges, a policy of 'watch and wait' is justified. For women with FXI levels between about 0.15 IU/ml and 0.70 IU/ml and a significant bleeding history or no previous haemo- static challenges, tranexamic acid is often used for 3 days, with the first dose being administered during labour. For women with severe FXI deficiency (FXI:C <0.10–0.20 IU/ml), FXI concentrate should be given during labour. Rarer clotting factor Deficiencies Inherited deficiencies of all of the clotting factors have been reported and these may result in haemorrhage at the time of delivery. These rare inherited coagulation disorders affect between 1:500 000— 1:2 000 000 of the population, although because they are recessively inherited they are significantly more common in countries where consanguineous relationships are found. Guidelines on the investi- gation and treatment of these rare disorders are available, including the management of delivery. Acquired FVIII inhibitors Acquired haemophilia is a rare disorder with an incidence of 1.5 per million per year. It is due to the formation of an autoantibody ('in- hibitor') that results in the depletion or inhibition of a coagulation factor, most commonly factor VIII, but antibodies to all of the co- agulation factors have been described. Acquired haemophilia A leads to a potentially severe bleeding diathesis, often of sudden onset. Although acquired haemophilia A presents most commonly in older people with a median age of 70–80 years, it can present in a younger age group and pregnancy is a recognized risk factor for the development of this disorder. The clinical features of acquired haemophilia A differ from those of congenital haemophilia in that bruising, soft tissue, muscle bleeding, gastrointestinal and urogenital bleeding are common manifestations, whereas haemarthroses are rare. Severe and life- threatening bleeding is common, but no haemostatic treatment is required in 25–33% of cases. The mortality associated with acquired haemophilia A has been reported to be between 7.9% and 42%. In women who are actively bleeding secondary to an auto-FVIII antibody, options for treatment include recombinant FVIIa and ac- tivated prothrombin complex concentrates. Elimination of the in- hibitor should be attempted using immunosuppression, which is initiated as soon as the diagnosis has been established. Where suc- cessful, this restores haemostasis to normal. Relapse of pregnancy-related acquired haemophilia appears to be relatively rare, but may occur and women should be warned of this possibility. The antibody may affect the factor VIII level of the fetus and this must be considered at the time of delivery. Miscellaneous haematological conditions Autoimmune neutropenia This is a rare disorder, most cases of which are mild. It can be pri- mary or secondary (in association with autoimmune disorders, sys- temic lupus erythematosus, or rheumatoid arthritis, viral infections, drugs). Symptomatic neutropenia (recurrent infections) occurs at neutrophil counts of below 0.5 × 109/litre. The main two risks during

 pregnancy are maternal sepsis, which can precipitate miscarriage or preterm labour, and neonatal neutropenia. Steroids are usually the first line of

treatment. Intravenous im- munoglobulin can be given if there is no response. Granulocyte- colony stimulating factor is used widely in the nonpregnant setting. There are concerns that it may be associated with increased preterm birth and a small increase in the incidence of venous thrombo- embolism, but there are case reports of its safe use in pregnancy. Myeloproliferative diseases Thrombosis and haemorrhage are the main cause of morbidity in pregnant patients with essential thrombocythemia and polycy- themia vera. There are limited data, but these conditions are dif- ficult to manage during pregnancy and are associated with a high fetal mortality. The live birth rate is approximately 60% in both essential thrombocythemia and polycythemia vera, with spontan- eous miscarriage during the first trimester being the most common complication and occurring in about 20–30% of all pregnancies. Intrauterine growth restriction, preterm delivery, and increased neonatal deaths have all been described. Major maternal complica- tions are more frequent, including major thromboses, post-partum haemorrhage, pre-eclampsia, and disseminated intravascular co- agulation. These are reduced with low-dose aspirin treatment. In high-risk pregnancies, the additional use of low molecular weight heparin and/or interferon α has also been beneficial. Such cases re- quire the close collaboration of obstetricians and haematologists, with attention to management of the thrombotic risk and increased fetal monitoring. FURTHER READING

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