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# CHAPTER 56: Hematological Disorders

*In the later months of pregnancy there is a slight increase in the amount of hemoglobin and red corpuscles and a slight increase in the number of white corpuscles, which become markedly accentuated during the first few days of the puerperium.*

—J. Whitridge Williams (1903)

## INTRODUCTION

There is virtually nothing from the first edition of Williams' 1903 textbook that addresses the common anemias of pregnancy. Only pernicious anemia is devoted two paragraphs to say it occasionally appeared in pregnancy. Today, it is well known that pregnant women are susceptible to hematological abnormalities that may affect any woman of childbearing age. These include chronic disorders such as hereditary anemias, immunological thrombocytopenia, and malignancies such as leukemias and lymphomas. Other disorders arise during pregnancy because of pregnancy-induced demands. Two examples are iron deficiency and megaloblastic anemias. Pregnancy may also unmask underlying hematological disorders. Finally, any hematological disease may first arise during pregnancy. Importantly, pregnancy induces physiological changes that often confuse the diagnosis of these hematological disorders and assessment of their treatment (Chap. 4, Hematological Changes).

## ANEMIAS

### Definition and Incidence

Normal values for concentrations of many cellular elements during pregnancy are listed in the Appendix (Serum and Blood Constituents). The Centers for Disease Control and Prevention (1998) defined anemia in iron-supplemented pregnant women using a cutoff of the 5th percentile—11 g/dL in the first and third trimesters, and 10.5 g/dL in the second trimester (Fig. 56-1). The modest fall in hemoglobin levels and hematocrit values during pregnancy is caused by a relatively greater expansion of plasma volume compared with the increase in red cell volume. The disproportion between the rates at which plasma and erythrocytes are added to the maternal circulation is greatest during the second trimester. Late in pregnancy, plasma expansion essentially ceases, while hemoglobin mass continues to accrue.

**FIGURE 56-1**

Mean hemoglobin concentrations (*black line*) and 5th and 95th percentiles (*blue lines*) for healthy pregnant women taking iron supplements. (Data from the Centers for Disease Control and Prevention, 1989.)

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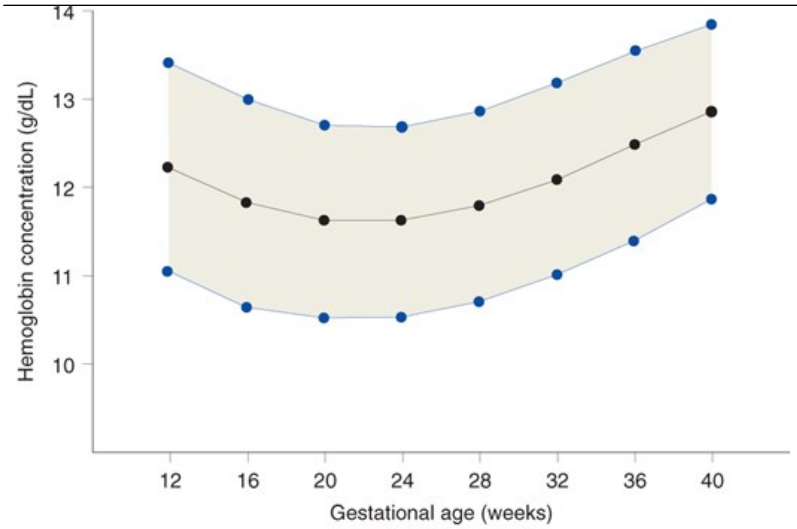


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The causes of more common anemias encountered in pregnancy are listed in Table 56-1. Their frequency is dependent on multiple factors such as geography, ethnicity, socioeconomic level, nutrition, preexisting iron status, and prenatal iron supplementation (American College of Obstetricians and Gynecologists, 2017a). In the United States, the prevalence of anemia in pregnancy is 3 to 38 percent (Centers for Disease Control and Prevention, 1989). In Latin America and the Caribbean, anemia prevalence ranges from 5 to 45 percent among women of childbearing age (Mujica-Coopman, 2015). Rates are also high in Israel, China, India, South Asia, and Africa (Azulay, 2015; Kumar, 2013, Stevens, 2013). Figure 56-2 highlights the global trends in hemoglobin concentrations and anemia thresholds in pregnant and nonpregnant women.

TABLE 56-1

**Causes of Anemia During Pregnancy**

| |
|---|
| **Acquired** |
| Iron-deficiency anemia |
| Anemia caused by acute blood loss |
| Anemia of inflammation or malignancy |
| Megaloblastic anemia |
| Acquired hemolytic anemia |
| Aplastic or hypoplastic anemia |
| **Hereditary** |
| Thalassemias |
| Sickle-cell hemoglobinopathies |
| Other hemoglobinopathies |
| Hereditary hemolytic anemias |

FIGURE 56-2

Global trends in hemoglobin concentrations in pregnant and nonpregnant women. (Reproduced with permission from Stevens GA, Finucane MM, De-Regil LM, et al: Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data, Lancet Glob Health. 2013 Jul;1(1):e16–25.)

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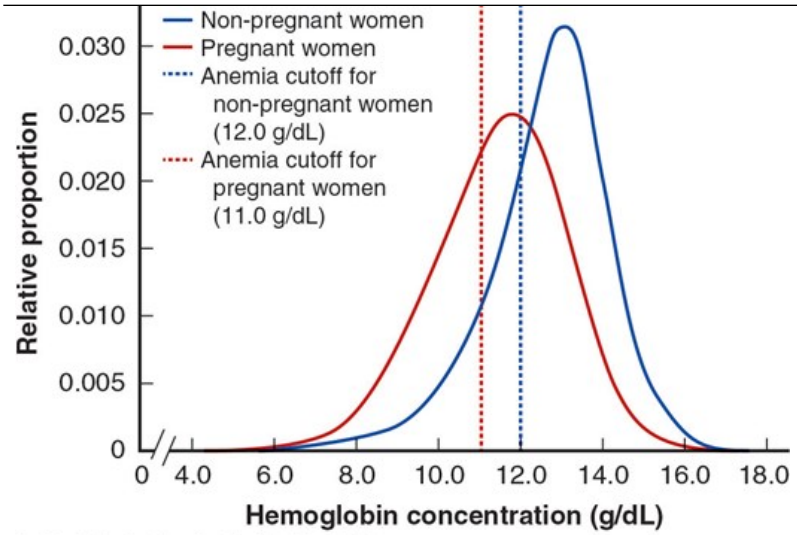


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## Effects on Pregnancy Outcomes

Most studies of anemia during pregnancy describe large populations and deal with nutritional anemias. Anemia is associated with several adverse pregnancy outcomes including preterm birth (Kidanto, 2009; Kumar, 2013; Rukuni, 2016). Children born to iron-deficient women and without iron supplementation are reported to have lower mental development scores (Drassinower, 2016; Tran, 2014).

A seemingly paradoxical finding is that healthy pregnant women with a higher hemoglobin concentration are also at greater risk for adverse perinatal outcomes (Murphy, 1986; von Tempelhoff, 2008). This may result from lower than average plasma volume expansion of pregnancy concurrent with normal red cell mass accrual. Scanlon and associates (2000) studied the relationship between maternal hemoglobin levels and rates of preterm or growth-restricted newborns in 173,031 pregnancies. Women whose hemoglobin concentration was three standard deviations *above* the mean at 12 or 18 weeks' gestation had a 1.3- to 1.8-fold greater incidence of fetal-growth restriction. Placental weight correlates negatively with maternal hemoglobin concentration (Larsen, 2016). These findings have led some to the illogical conclusion that withholding iron supplementation to cause iron-deficiency anemia will improve pregnancy outcomes (Ziaei, 2007).

## Iron-Deficiency Anemia

The two most common causes of anemia during pregnancy and the puerperium are iron deficiency and acute blood loss. In a study of more than 1300 women, 21 percent had third-trimester anemia, and 16 percent had iron-deficiency anemia (Vandevijvere, 2013). In a typical singleton gestation, the maternal need for iron averages nearly 1000 mg. Multifetal gestational requirements are considerably higher (Ru, 2016). These amounts exceed the iron stores of most women and result in iron-deficiency anemia unless supplementation is given.

Iron deficiency is often manifested by an appreciable drop in hemoglobin concentration. In the third trimester, additional iron is needed to augment maternal hemoglobin and for transport to the fetus. Because the amount of iron diverted to the fetus is similar in a normal and in an iron-deficient mother, the newborn of a severely anemic mother does not suffer from iron-deficiency anemia. Neonatal iron stores are related to maternal iron status and to timing of cord clamping.

### Diagnosis

Classic morphological evidence of iron-deficiency anemia is erythrocyte hypochromia and microcytosis (Fig. 56-3). This may be less prominent in the pregnant woman. Serum ferritin levels are lower. And, levels of *hepcidin*—the master regulator of iron availability—are decreased normally in pregnancy. With iron deficiency, hepcidin levels follow those of serum ferritin (Camaschella, 2015; Koenig, 2014).

**FIGURE 56-3**

This peripheral blood smear from a women with iron-deficiency anemia contains many scattered microcytic and hypochromic red cells with

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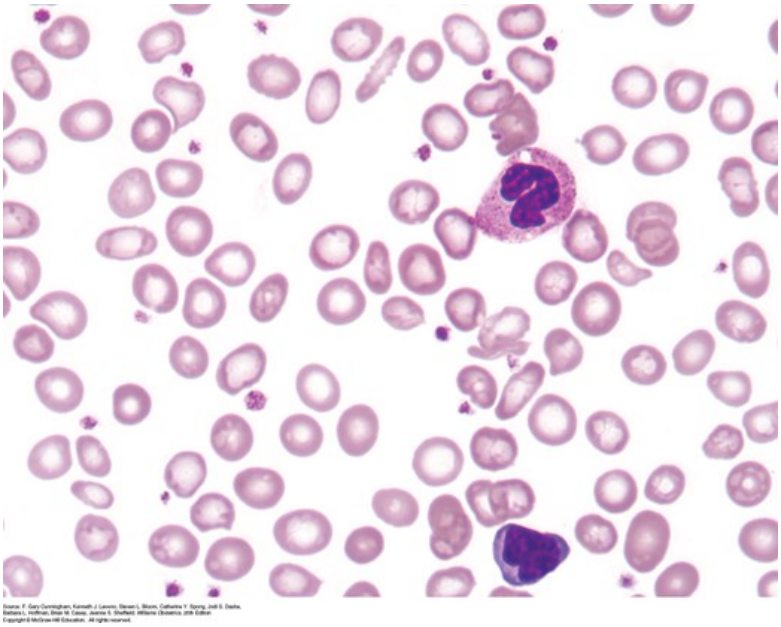
characteristic central pallor. These exhibit moderate anisopoikilocytosis, namely, varying sizes and shapes including occasional elliptocytes, which can be oval or pencil-shaped. (Reproduced with permission from Werner CL, Richardson DL, Chang SY, et al (eds): Perioperative Considerations. In Williams Gynecology Study Guide, 3rd ed. New York, McGraw-Hill Education, 2016: Photo contributor: Dr. Weina Chen.)



The initial evaluation of a pregnant woman with moderate anemia includes measurements of hemoglobin, hematocrit, and red cell indices; careful examination of a peripheral blood smear; a sickle-cell preparation if the woman has African origin; and evaluation of serum iron or ferritin levels, or both (Appendix, Serum and Blood Constituents). Serum ferritin levels normally decline during pregnancy, and levels <10 to 15 mg/L confirm iron-deficiency anemia.

When pregnant women with moderate iron-deficiency anemia are given adequate iron therapy, a hematological response is detected by an elevated reticulocyte count. The rate of rise of hemoglobin concentration or hematocrit is typically slower than in nonpregnant women due to the increasing and larger blood volumes during pregnancy.

### Treatment

Routinely in pregnancy, daily oral supplementation with 30 to 60 mg of elemental iron and 400 µg of folic acid is recommended (World Health Organization, 2012). A Cochrane review found that intermittent oral iron supplementation may also be appropriate (Peña-Rosas, 2015). For iron-deficiency anemia, resolution and restitution of iron stores can be accomplished with simple iron salts that provide approximately 200 mg daily of *elemental iron*. These include ferrous sulfate, fumarate, or gluconate. If a woman cannot or will not take oral iron preparations, then parenteral therapy is given. Although both are administered intravenously, ferrous sucrose is safer than iron-dextran (American College of Obstetricians and Gynecologists, 2017a; Camaschella, 2015; Shi, 2015). Hemoglobin and ferritin levels show equivalent rises in women treated with either oral or parenteral iron therapy (Breymann, 2017; Daru, 2016).

## Anemia from Acute Blood Loss

In early pregnancy, anemia caused by acute blood loss is common with abortion, ectopic pregnancy, and hydatidiform mole. Postpartum, anemia commonly stems from obstetrical hemorrhage. Massive hemorrhage demands immediate treatment as described in Chapter 41 (Hypovolemic Shock). If a moderately anemic woman—defined by a hemoglobin value of approximately 7 g/dL—is hemodynamically stable, is able to ambulate without adverse symptoms, and is not septic, then blood transfusions are not indicated. Instead, oral iron therapy is given for at least 3 months (Krafft, 2005).

## Anemia Associated with Chronic Disease

Various disorders, such as chronic renal insufficiency, cancer and chemotherapy, human immunodeficiency virus (HIV) infection, and chronic inflammation result in moderate and sometimes severe anemia, usually with slightly hypochromic and microcytic erythrocytes. It is the second most

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common form of anemia worldwide (Weiss, 2005).

During pregnancy, women with chronic disorders may develop anemia for the first time. In those with preexisting anemia, it may be intensified as plasma volume expands. Causes include chronic renal insufficiency, inflammatory bowel disease, and connective-tissue disorders. Others are granulomatous infections, malignant neoplasms, rheumatoid arthritis, and chronic suppurative conditions.

Chronic renal insufficiency is the most common disorder that we have encountered as a cause of this type of anemia during pregnancy. Some cases are accompanied by erythropoietin deficiency. As discussed in Chapter 53 (Chronic Kidney Disease), during pregnancy in women with mild chronic renal insufficiency, the degree of red cell mass expansion is inversely related to renal impairment. At the same time, plasma volume expansion usually is normal, and thus anemia is intensified (Cunningham, 1990).

For treatment, adequate iron stores must be ensured. *Recombinant erythropoietin* has been used successfully to treat anemia stemming from chronic disease (Weiss, 2005). In pregnancies complicated by chronic renal insufficiency, recombinant erythropoietin is usually considered when the hematocrit approximates 20 percent (Cyganek, 2011; Ramin, 2006). One worrisome side effect of this agent is hypertension, which is already prevalent in women with renal disease. Red cell aplasia and antierythropoietin antibodies have also been reported (Casadevall, 2002; McCoy, 2008).

## Megaloblastic Anemia

These anemias are characterized by blood and bone-marrow abnormalities from impaired DNA synthesis. This leads to large cells with arrested nuclear maturation, whereas the cytoplasm matures more normally. Worldwide, the prevalence of megaloblastic anemia during pregnancy varies considerably. It is rare in the United States.

### Folic Acid Deficiency

Megaloblastic anemia developing during pregnancy almost always results from folic acid deficiency. In the past, this condition was referred to as *pernicious anemia of pregnancy*. It usually is found in women who do not consume fresh green leafy vegetables, legumes, or animal protein. As folate deficiency and anemia worsen, anorexia often becomes intense and further aggravates the dietary deficiency. Drugs and excessive ethanol ingestion either cause or contribute (Hesdorffer, 2015).

In nonpregnant women, the folic acid requirement is 50 to 100 µg/d. During pregnancy, requirements are increased, and 400 µg/d is recommended. The earliest biochemical evidence is low plasma folic acid concentrations (Appendix, Serum and Blood Constituents). Early morphological changes usually include neutrophils that are hypersegmented and newly formed erythrocytes that are macrocytic. With preexisting iron deficiency, macrocytic erythrocytes cannot be detected by measurement of the mean corpuscular volume. Careful examination of a peripheral blood smear, however, usually demonstrates some macrocytes. As the anemia becomes more intense, peripheral nucleated erythrocytes appear, and bone marrow examination discloses megaloblastic erythropoiesis. Anemia may then become severe, and thrombocytopenia, leukopenia, or both may develop. The fetus and placenta extract folate from maternal circulation so effectively that the fetus is not anemic despite severe maternal anemia.

For treatment, folic acid is given along with iron, and a nutritious diet is encouraged. By 4 to 7 days after beginning folic acid treatment, the reticulocyte count is increased, and leukopenia and thrombocytopenia are corrected.

For prevention of megaloblastic anemia, a diet should contain sufficient folic acid. The role of folate deficiency in the genesis of neural-tube defects has been well studied (Chap. 13, Genetic Tests). Since the early 1990s, nutritional experts and the American College of Obstetricians and Gynecologists (2016a) have recommended that all women of childbearing age consume at least 400 µg of folic acid daily. More folic acid is given with multifetal pregnancy, hemolytic anemia, Crohn disease, alcoholism, and inflammatory skin disorders. Women with a family history of congenital heart disease may also benefit from higher doses (Huhta, 2015). Women who previously have had infants with neural-tube defects have a lower recurrence rate if a daily 4-mg folic acid supplement is given.

### Vitamin $B_{12}$ Deficiency

During pregnancy, vitamin $B_{12}$ levels are lower than nonpregnant values because of decreased levels of binding proteins, namely, the transcobalamins. During pregnancy, megaloblastic anemia is rare from deficiency of vitamin $B_{12}$, that is, cyanocobalamin. Instead, a typical example is *Addisonian*

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*pernicious anemia,* which results from absent intrinsic factor that is requisite for dietary vitamin $B_{12}$ absorption. This autoimmune disorder usually has its onset after age 40 years (Stabler, 2013).

In our limited experience, vitamin $B_{12}$ deficiency in pregnancy is more likely encountered following gastric resection. Those who have undergone total gastrectomy require 1000 µg of vitamin $B_{12}$ given intramuscularly each month. Those with a partial gastrectomy usually do not need supplementation, but adequate serum vitamin $B_{12}$ levels should be ensured (Appendix, Serum and Blood Constituents). Other causes of megaloblastic anemia from vitamin $B_{12}$ deficiency include Crohn disease, ileal resection, some drugs, and bacterial overgrowth in the small bowel (Hesdorffer, 2015; Stabler, 2013).

## Hemolytic Anemia

Several conditions feature accelerated erythrocyte destruction. Damage may be stimulated by a congenital red-cell abnormality or in other cases by antibodies directed against red-cell membrane proteins. Hemolysis may be the primary disorder, and sickle-cell disease and hereditary spherocytosis are examples. In other cases, hemolysis develops secondary to an underlying condition such as systemic lupus erythematosus or preeclampsia. Microangiopathic hemolytic anemia due to malignancy has been reported in pregnancy (Happe, 2016).

### Autoimmune Hemolysis

The cause of aberrant antibody production is unknown. Typically, both the direct and indirect antiglobulin (Coombs) tests are positive. Anemias caused by these factors may be due to warm-active autoantibodies (80 to 90 percent), cold-active antibodies, or a combination. These syndromes also may be classified as primary (idiopathic) or secondary due to underlying diseases or other factors. Examples of the latter include lymphomas and leukemias, connective-tissue diseases, infections, chronic inflammatory diseases, and drug-induced antibodies (Provan, 2000). *Cold-agglutinin disease* may be induced by infectious etiologies such as *Mycoplasma pneumoniae* or Epstein-Barr viral mononucleosis (Dhingra, 2007). Hemolysis and positive antiglobulin test results may be the consequence of either immunoglobulin M (IgM) or immunoglobulin G (IgG) antierythrocyte antibodies. When thrombocytopenia is comorbid, it is termed *Evans syndrome* (Wright, 2013).

In pregnancy, hemolysis can be markedly accelerated. Rituximab, along with prednisone, is first-line treatment (Luzzatto, 2015). Coincidental thrombocytopenia usually corrects with therapy. Transfusion of red cells is complicated by antierythrocyte antibodies, but warming the donor cells to body temperature may decrease their destruction by cold agglutinins.

### Drug-Induced Hemolysis

These hemolytic anemias must be differentiated from other causes of autoimmune hemolysis. In most cases, hemolysis is mild, it resolves with drug withdrawal, and recurrence is prevented by avoidance of the drug. One mechanism is hemolysis induced through drug-mediated immunological injury to red cells. The drug may act as a high-affinity hapten when bound to a red-cell protein to which antidrug antibodies attach—for example, IgM antipenicillin or anticephalosporin antibodies. Some other drugs act as low-affinity haptens and adhere to cell membrane proteins. Examples include probenecid, quinidine, rifampin, and thiopental. A more common mechanism for drug-induced hemolysis is related to a congenital erythrocyte enzymatic defect. An example is glucose-6-phosphate dehydrogenase deficiency, which is common in African-American women and discussed later (Aplastic and Hypoplastic Anemia).

Drug-induced hemolysis is usually chronic and mild to moderate, but occasionally acute hemolysis is severe. Garratty and coworkers (1999) described seven women with severe Coombs-positive hemolysis stimulated by cefotetan given as prophylaxis for obstetrical procedures. Alpha-methyldopa can cause similar hemolysis (Grigoriadis, 2013). Moreover, maternal hemolysis has been reported after intravenous immune globulin therapy (Rink, 2013). Withdrawal of the offending drug frequently halts the hemolysis.

### Pregnancy-Induced Hemolysis

Unexplained severe hemolytic anemia can develop during early pregnancy, and it resolves within months postpartum. A clear immune mechanism or red cell defects are not contributory (Starksen, 1983). Because the fetus-neonate also may demonstrate transient hemolysis, an immunological cause is suspected. Maternal corticosteroid treatment is often—but not always—effective (Kumar, 2001). We have cared for a woman who during each pregnancy developed intense severe hemolysis with anemia that was controlled by prednisone. Her fetuses were not affected, and in all instances,

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hemolysis abated spontaneously after delivery.

### Pregnancy-Associated Hemolysis

In some cases, hemolysis is induced by conditions unique to pregnancy. Mild microangiopathic hemolysis with thrombocytopenia is relatively common with severe preeclampsia and eclampsia (Cunningham, 2015; Kenny, 2015). This HELLP (*hemolysis, elevated liver enzyme levels, low platelet count*) syndrome is discussed in Chapter 40 (Maternal Thrombocytopenia). Another is acute fatty liver of pregnancy, which is associated with moderate to severe hemolytic anemia (Nelson, 2013). It is discussed in Chapter 55 (Acute Fatty Liver of Pregnancy).

### Paroxysmal Nocturnal Hemoglobinuria

Although commonly regarded as a hemolytic anemia, this hemopoietic stem cell disorder is characterized by formation of defective platelets, granulocytes, and erythrocytes. Paroxysmal nocturnal hemoglobinuria is acquired and arises from one abnormal clone of cells, much like a neoplasm (Luzzatto, 2015). One mutated X-linked gene responsible for this condition is termed *PIG-A* because it codes for phosphatidylinositol glycan protein A. Resultant abnormal anchor proteins of the erythrocyte and granulocyte membrane make these cells unusually susceptible to lysis by complement (Provan, 2000). The most serious complication is thrombosis, which is heightened in the hypercoagulable state of pregnancy.

Chronic hemolysis has an insidious onset, and its severity ranges from mild to lethal. Hemoglobinuria develops at irregular intervals and is not necessarily nocturnal. Hemolysis may be initiated by transfusions, infections, or surgery. Almost 40 percent of patients suffer venous thromboses and may also experience renal failure, hypertension, and Budd-Chiari syndrome. Because of the thrombotic risk, prophylactic anticoagulation is recommended (Parker, 2005). The treatment of choice is eculizumab, an antibody that inhibits complement activation (Kelly, 2015). Median survival after diagnosis is 10 years, and bone marrow transplantation is the definitive treatment.

During pregnancy, paroxysmal nocturnal hemoglobinuria can be serious and unpredictable. Complications have been reported in up to three fourths of affected women, and the maternal mortality rate in the past was 10 to 20 percent (De Gramont, 1987; de Guibert, 2011). Complications more often develop postpartum, and half of affected women develop venous thrombosis (Fieni, 2006; Ray, 2000). Kelly and colleagues (2015) described 75 pregnancies in 61 affected women treated with eculizumab. In half of these, the dose was increased during pregnancy. They described no maternal deaths but 4 percent stillbirths.

### Bacterial Toxins

The most fulminant acquired hemolytic anemia encountered during pregnancy is caused by the exotoxin of *Clostridium perfringens* or by group A β-hemolytic streptococcus (Chap. 47, Clinical Manifestations). Endotoxin of gram-negative bacteria, that is, lipopolysaccharide, may be accompanied by hemolysis and mild-to-moderate anemia (Cox, 1991). For example, anemia often accompanies acute pyelonephritis. With normal erythropoietin production, red cell mass is restored following infection resolution as pregnancy progresses (Cavenee, 1994; Dotters-Katz, 2013).

### Inherited Erythrocyte Membrane Defects

The normal erythrocyte is a flexible biconcave disc that allows numerous cycles of reversible deformations. Several genes encode expression of erythrocyte structural membrane proteins or intraerythrocytic enzymes. Various mutations of these genes may result in inherited membrane defects or enzyme deficiencies that destabilize the lipid bilayer. The loss of lipids from the erythrocyte membrane causes a surface area deficiency and poorly deformable cells that undergo hemolysis. Anemia severity depends on the degree of rigidity or decreased distensibility. Erythrocyte morphology similarly is dependent on these factors, and these disorders are usually named after the most dominant red-cell shape characteristic of the disorder. Three examples are *hereditary spherocytosis, pyropoikilocytosis,* and *ovalocytosis.*

#### Hereditary Spherocytosis

Hemolytic anemias that compose this group of inherited membrane defects are among the most common hemolytic anemias found in gravidas. Mutations are usually an autosomally dominant, variably penetrant *spectrin* deficiency. Others are autosomally recessive or de novo gene mutations that result from deficiency of ankyrin, protein 4.2, moderate band 3, or combinations of these (Gallagher, 2010; Rencic, 2017; Yawata, 2000). The degrees of anemia and jaundice vary, and diagnosis is confirmed by identification of spherocytes on peripheral smear and increased osmotic fragility.

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Spherocytic anemias may be associated with a so-called crisis that is characterized by severe anemia from accelerated hemolysis, and it develops in patients with an enlarged spleen. Infection can also accelerate hemolysis or suppress erythropoiesis to worsen anemia. An example of the latter is infection with parvovirus B19 (Chap. 64, Respiratory Viruses). In severe cases, splenectomy reduces hemolysis, anemia, and jaundice.

#### Pregnancy

In general, women with inherited red-cell membrane defects do well during pregnancy. Folic acid supplementation of 4 mg daily is given orally to sustain erythropoiesis. Women with hereditary spherocytosis cared for at Parkland Hospital had hematocrits ranging from 23 to 41 volumes percent—mean 31 (Maberry, 1992). Reticulocyte counts ranged from 1 to 23 percent. Among 50 pregnancies in 23 women, eight women miscarried. Four of 42 infants were born preterm, but none was growth restricted. Infection in four women intensified hemolysis, and three of these required transfusions. Similar results were reported by Pajor and coworkers (1993).

Because these disorders are inherited, the newborn may be affected. Celkan and Alhaj (2008) report prenatal diagnosis via cordocentesis at 18 weeks' gestation and testing for osmotic fragility. Newborns with hereditary spherocytosis may manifest hyperbilirubinemia and anemia shortly after birth.

### Erythrocyte Enzyme Deficiencies

An intraerythrocytic deficiency of enzymes that permit anaerobic glucose metabolism may cause *hereditary nonspherocytic anemia.* Most of these mutations are autosomal recessive traits. As discussed earlier (Hemolytic Anemia), most episodes of severe anemia with enzyme deficiencies are induced by drugs or infections.

*Pyruvate kinase* deficiency is associated with variable anemia and hypertensive complications (Wax, 2007). Due to recurrent transfusions in homozygous carriers, iron overload is frequent, and associated myocardial dysfunction should be monitored (Dolan, 2002). The fetus that is homozygous for this mutation may develop *hydrops fetalis* from anemia and heart failure (Chap. 15, Hydrops Fetalis).

*Glucose-6-phosphate dehydrogenase (G6PD) deficiency* is complex because there are more than 400 known enzyme variants. The most common are caused by a base substitution that leads to an amino acid replacement and a broad range of phenotypic severity (Luzzatto, 2015; Puig, 2013). In the homozygous or A variant, both X chromosomes are affected, and erythrocytes are markedly deficient in G6PD activity. Approximately 2 percent of African-American women are affected, and the heterozygous variant is found in 10 to 15 percent (Mockenhaupt, 2003). In both instances, random X-chromosome inactivation—*lyonization*—results in variable enzyme activity.

During pregnancy, infections or drugs can induce hemolysis in G6PD deficiency heterozygotes or homozygotes, and severity is related to enzyme activity. Anemia is usually episodic, although some variants induce chronic nonspherocytic hemolysis. Because young erythrocytes contain more enzyme activity, anemia ultimately stabilizes and is corrected soon after the inciting cause is eliminated. Newborn screening for G6PD deficiency is not recommended by the American College of Obstetricians and Gynecologists (2016b).

## Aplastic and Hypoplastic Anemia

Aplastic anemia is a grave complication that is characterized by pancytopenia and markedly hypocellular bone marrow (Young, 2015). There are multiple etiologies, and at least one is linked to autoimmune diseases (Stalder, 2009). The inciting cause can be identified in approximately a third of cases. These include drugs and other chemicals, infection, irradiation, leukemia, immunological disorders, and inherited conditions such as *Fanconi anemia* and *Diamond-Blackfan syndrome* (Green, 2009; Lipton, 2009). The functional defect appears to be a marked decrease in committed marrow stem cells.

Hematopoietic stem-cell transplantation is optimal therapy in a young patient (Killick, 2016). Immunosuppressive therapy is given, and in some nonresponders, *eltrombopag* has been successful (Olnes, 2012; Townsley, 2017). Definitive treatment is bone marrow transplantation, and approximately three fourths of patients have a good response and long-term survival (Rosenfeld, 2003). Umbilical cord blood-derived stem cells can also serve as a potential transplant source (Moise, 2005; Pinto, 2008). Previous blood transfusions and even pregnancy enhance the risk of graft rejection (Young, 2015).

### Pregnancy

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Hypoplastic or aplastic anemia complicating pregnancy is rare. A study of 60 pregnancies complicated by aplastic anemia found that half were diagnosed during pregnancy (Bo, 2016). There are a few well-documented cases of *pregnancy-induced hypoplastic anemia,* and the anemia and other cytopenias improve or remit following delivery or pregnancy termination (Bourantas, 1997; Choudhry, 2002). In some cases, anemia recurred in a subsequent pregnancy.

*Diamond-Blackfan anemia* is a rare form of pure red-cell hypoplasia. Approximately 40 percent of cases are familial and have autosomal dominant inheritance (Orfali, 2004). The response to glucocorticoid therapy is usually good. Continuous treatment is necessary, and most become at least partially transfusion dependent (Vlachos, 2008). In 64 pregnancies complicated by this syndrome, Faivre and associates (2006) reported that two thirds had problems related to placental vascular etiologies that included miscarriage, preeclampsia, preterm birth, fetal-growth restriction, or stillbirth.

*Gaucher disease* is an autosomally recessive lysosomal enzyme deficiency characterized by deficient activity of *acid* β-*glucosidase*. Affected women have anemia and thrombocytopenia that is usually worsened by pregnancy (Granovsky-Grisaru, 1995). Elstein and colleagues (1997) described six pregnant women whose disease improved when they were given *alglucerase* enzyme replacement. *Imiglucerase* therapy, which is human recombinant enzyme replacement therapy, has been available since 1994. European guidelines recommend treatment in pregnancy, whereas the Food and Drug Administration states it may be given with “clear indications” (Granovsky-Grisaru, 2011).

The major risks with hypoplastic anemia are hemorrhage and infection. Rates of preterm labor, preeclampsia, fetal-growth restriction, and stillbirth are increased (Bo, 2016). Management depends on gestational age, and supportive care includes continuous infection surveillance and prompt antimicrobial therapy. Granulocyte transfusions are given only during infections. Red cells are transfused to improve symptomatic anemia and routinely to maintain the hematocrit at or above 20 volumes percent. Platelet transfusions may be needed to control hemorrhage. Maternal mortality rates reported since 1960 have averaged nearly 50 percent, however, better outcomes have been reported more recently (Choudhry, 2002; Kwon, 2006).

#### Pregnancy after Bone Marrow Transplantation

Several reports describe successful pregnancies in women who have undergone bone marrow transplantation (Borgna-Pignatti, 1996; Eliyahu, 1994). In their review, Sanders and coworkers (1996) reported 72 pregnancies in 41 women who had undergone transplantation. In the 52 pregnancies resulting in a liveborn neonate, almost half were complicated by preterm delivery or hypertension. Our experiences with a few of these women indicate that they have normal pregnancy-augmented erythropoiesis and total blood volume expansion.

## POLYCYTHEMIAS

### Secondary Polycythemia

Excessive erythrocytosis during pregnancy is usually related to chronic hypoxia from maternal congenital cardiac disease or a chronic pulmonary disorder. Unusually heavy cigarette smoking can cause polycythemia. We have encountered otherwise healthy pregnant women who were heavy smokers, had chronic bronchitis, and had hematocrits ranging from 55 to 60 volumes percent! If polycythemia is severe, the probability of a successful pregnancy outcome is low.

### Polycythemia Vera

This is a primary clonal myeloproliferative hemopoietic stem-cell disorder characterized by excessive proliferation of erythroid, myeloid, and megakaryocytic precursors (Spivak, 2015; Vannucchi, 2015). Virtually all patients have either a *JAK2*V617F or a *JAK2* exon 12 gene mutation (Harrison, 2009). Symptoms are related to increased blood viscosity, and thrombotic complications are common. Treatment of nonpregnant patients is with hydroxyurea or ruxolitinib (Vannucchi, 2015).

Fetal loss rates are high in women with polycythemia vera, and pregnancy outcome may be improved with aspirin therapy (Griesshammer, 2006; Robinson, 2005; Tefferi, 2000). Women with a history of venous thrombosis are given prophylaxis with low-molecular-weight heparin. If cytoreduction is required during pregnancy, interferon alpha may be considered (Kreher, 2014).

## HEMOGLOBINOPATHIES

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## Sickle-Cell Hemoglobinopathies

Hemoglobin A is the most common hemoglobin tetramer and consists of two α- and two β-chains. In contrast, sickle hemoglobin (hemoglobin S) originates from a single β-chain substitution of glutamic acid by valine, which stems from an A-for-T substitution at codon 6 of the β-globin gene. Hemoglobinopathies that can result in clinical features of the *sickle-cell syndrome* include sickle-cell anemia (Hb SS); sickle-cell hemoglobin C disease (Hb SC); sickle-cell β-thalassemia disease (either Hb S/$B^0$ or Hb S/$B^+$); and sickle-cell E disease (Hb SE) (Benz, 2015). All are also associated with increased pregnancy morbidity.

Sickle-cell anemia results from the inheritance of the gene for S hemoglobin from each parent. In the United States, 1 of 12 African-Americans has sickle-cell trait, which results from inheritance of one gene for hemoglobin S and one for normal hemoglobin A. The computed incidence of sickle-cell anemia among African-Americans is 1 in 576 (1/12 × 1/12 × 1/4 = 1/576). But, the disease is less common in adults because of earlier mortality. Hemoglobin C originates from a single β-chain substitution of glutamic acid by lysine, which stems from a T-for-C substitution at codon 6 of the β-globin gene. Approximately 1 in 40 African-Americans has the gene for hemoglobin C. Thus, the theoretical incidence for coinheritance of the gene for hemoglobin S and an allelic gene for hemoglobin C in an African-American child is about 1 in 2000 (1/12 × 1/40 × 1/4). β-Thalassemia minor is approximately 1 in 40, thus S-β-thalassemia also is found in approximately 1 in 2000 (1/12 × 1/40 × 1/4).

### Pathophysiology

Red cells with hemoglobin S undergo sickling when they are deoxygenated, and the hemoglobin aggregates. Constant sickling and unsickling cause membrane damage, and the cell may become irreversibly sickled. Events that slow erythrocyte transit through the microcirculation include adhesion to endothelial cells, erythrocytic dehydration, and vasomotor dysregulation. Clinically, the hallmarks of sickling episodes are periods during which there is ischemia and infarction in various organs. The *sickle-cell crisis* produces clinical symptoms, predominately pain, which is often severe. There may be aplastic, megaloblastic, sequestration, and hemolytic crises.

Chronic and acute changes from sickling include bony abnormalities such as osteonecrosis of femoral and humeral heads, renal medullary damage, autosplenectomy in homozygous SS patients and splenomegaly in other variants, hepatomegaly, ventricular hypertrophy, pulmonary infarctions, pulmonary hypertension, cerebrovascular accidents, leg ulcers, and a propensity for infection and sepsis (Benz, 2015; Gladwin, 2004). Other sequelae are cerebrovascular aneurysms and sickle-cell vasculopathy (Buonanno, 2016). Pulmonary hypertension can develop and is found in 20 percent of adults with SS hemoglobin (Gladwin, 2008).

### Treatment

Good supportive care is essential to prevent mortality. Specific therapies are evolving, and many are still experimental. One treatment is hemoglobin F induction with drugs that stimulate gamma-chain synthesis. This increases hemoglobin F, which inhibits hemoglobin S polymerization. One example is *hydroxyurea,* which augments hemoglobin F production and reduces the number of sickling episodes (Platt, 2008). Hydroxyurea is teratogenic in animals, although a preliminary 17-year surveillance of antenatally exposed children was reassuring (Ballas, 2009; Briggs, 2015; Italia, 2010). A randomized trial showed no benefit from treatment with *prasugrel*, a platelet inhibitor (Henney, 2016). Treatment with *crizanlizumab*, an antibody against P-selectin, significantly lowered the incidence of adverse events (Ataga, 2017).

Various forms of hemopoietic cell transplantation are emerging as “cures” for sickle-cell syndromes and severe thalassemias (Hsieh, 2009). Oringanje and coworkers (2013) performed a Cochrane review and found that only observational studies have been reported. *Bone marrow transplantation* has 5-year survival rates that exceed 90 percent (Dalle, 2013). *Cord-blood stem-cell transplantation* from related donors also shows great promise (Shenoy, 2013). Finally, successful gene therapy has been accomplished by lentiviral vector-mediated addition of a beta globin gene into stem cells (Ribeil, 2017).

### Pregnancy and Sickle-Cell Syndromes

Pregnancy is a serious burden to women with any of the major sickle hemoglobinopathies, particularly those with hemoglobin SS disease. Several large studies have defined this relationship. Villers and colleagues (2008) studied 17,952 births in women with sickle-cell syndromes. Chakravarty and associates (2008) studied 4352 pregnancies. A more recent cohort study of 1526 women was reported by Boulet and coworkers (2013). Last, a cohort study taken from more than 2 million women compared those with sickle-cell disease to normal controls (Kuo, 2016). Common obstetrical and medical complications and their relative risks from a composite of most of these studies are shown in Table 56-2.

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TABLE 56-2

**Pregnancy Morbidity with Hemoglobin SS and SC Disease**

| | Odds Ratios | |
|---|---|---|
| **Outcome** | **Hb SS** | **Hb SC** |
| Preeclampsia | 2–3.1 | 2.0 |
| Stillbirth | 6.5 | 3.2 |
| Preterm delivery | 2–2.7 | 1.5 |
| Growth restriction | 2.8–3.9 | 1.5 |
| Maternal mortality | 11–23 | 11 |

Data from metaanalyses by Boafor, 2016; Oteng-Ntim, 2015.

Maternal morbidity common in pregnancy includes ischemic necrosis of multiple organs, especially bone marrow that causes episodes of severe pain. Pyelonephritis, pneumonia, and pulmonary complications are frequent. Although the maternal mortality rate has improved, perinatal morbidity and mortality rates remain formidable (Boga, 2016; Lesage, 2015; Yu, 2009). Perinatal outcomes include increased risks for preterm birth, fetal-growth restriction, and perinatal mortality.

### Hemoglobin SC

In nonpregnant women, morbidity and mortality rates from SC disease are appreciably lower than those from sickle-cell anemia. Indeed, fewer than half of these women have symptoms before pregnancy. In our experiences, affected gravidas suffer attacks of severe bone pain and episodes of pulmonary infarction and embolization more commonly than when they are not pregnant (Cunningham, 1983). Some adverse pregnancy outcomes are shown in Table 56-2.

### Management During Pregnancy

Women with sickle-cell hemoglobinopathies require close prenatal observation. Any factor that impairs erythropoiesis or increases red cell destruction aggravates the anemia. Prenatal folic acid supplementation with 4 mg daily is needed to support rapid red blood cell turnover.

One danger is that a symptomatic woman may categorically be considered to be suffering from a “sickle-cell crisis.” As a result, serious obstetrical or medical problems that cause pain, anemia, or both may be overlooked. Examples are ectopic pregnancy, placental abruption, pyelonephritis, or appendicitis. Thus, a diagnosis of sickle-cell crisis should be applied only after all other possible causes have been excluded. Pain with sickle-cell syndromes is caused by intense sequestration of sickled erythrocytes and infarction in various organs, especially bone marrow. These episodes may develop acutely, especially late in pregnancy, during labor and delivery, and early in the puerperium.

Guidelines for care of these women have been appropriately stressed by Rees and colleagues (2003). Marti-Carvajal and coworkers (2009) performed a Cochrane review and reported that no randomized trials have evaluated treatment during pregnancy. At minimum, intravenous fluids are given, and opioids are administered promptly for severe pain. Oxygen via nasal cannula may decrease the intensity of sickling at the capillary level. We have found that red cell transfusions after the onset of severe pain do not dramatically improve pain intensity and may not shorten its duration. Conversely, as discussed later, prophylactic transfusions almost always prevent further vasoocclusive episodes and pain crises. Recent reports suggest benefits from epidural analgesia (Verstraete, 2012; Winder, 2011). Long term, affected women can become habituated to narcotics. This problem is highlighted by the increased rates of neonatal abstinence syndrome, which is a constellation of withdrawal symptoms (Shirel, 2016).

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Rates of covert bacteriuria and acute pyelonephritis are elevated substantively, and screening and treatment for bacteriuria are essential. If pyelonephritis develops, sickle cells are extremely susceptible to bacterial endotoxin, which can cause dramatic and rapid red cell destruction while simultaneously suppressing erythropoiesis. Pneumonia, especially due to *Streptococcus pneumoniae,* is common. The Centers for Disease Control and Prevention recommends specific vaccination for those with sickle-cell disease and all asplenic patients (Kim, 2016). These are polyvalent pneumococcal, *Haemophilus influenzae* type B, and meningococcal vaccines, and administration guidelines are found in Table 9-7.

Pulmonary complications are frequent. Of these, *acute chest syndrome* is characterized by pleuritic chest pain, fever, cough, lung infiltrates, and hypoxia, and usually also by bone and joint pain (Vichinsky, 2000). In addition to symptoms, radiographs show a new pulmonary infiltrate. There are four precipitants: infection, marrow emboli, thromboembolism, and atelectasis (Medoff, 2005). Bacterial or viral infection causes approximately half of cases. When acute chest syndrome develops, the mean duration of hospitalization is 10.5 days. Mechanical ventilation is required in approximately 15 percent, and the mortality rate approximates 3 percent (Gladwin, 2008). At least for nonpregnant adults, some recommend rapid simple or exchange transfusions to remove the “trigger” for acute chest syndromes (Gladwin, 2008). In a study of nonpregnant patients, Turner and colleagues (2009) reported that there were no increased benefits of exchange versus simple transfusions, and the former were associated with fourfold increased blood usage.

Women with sickle-cell disease usually have some degree of *cardiac dysfunction* from ventricular hypertrophy. Chronic hypertension worsens the dysfunction (Gandhi, 2000). During pregnancy, the basal hemodynamic state characterized by high cardiac output and increased blood volume is augmented (Veille, 1994). Although most women tolerate pregnancy without problems, complications such as severe preeclampsia or serious infections may result in ventricular failure (Cunningham, 1986). Heart failure caused by pulmonary hypertension must also be considered (Chakravarty, 2008).

In 4352 pregnancies in women with sickle-cell syndromes, Chakravarty and associates (2008) reported significantly higher pregnancy complication rates. Compared with controls, women with sickling disorders had a 63-percent rate of nondelivery-related admissions. They had a 1.8-fold greater incidence of hypertensive disorders—19 percent; a 2.9-fold higher rate of fetal-growth restriction—6 percent; and a 1.7-fold increased cesarean delivery rate—45 percent.

#### Prophylactic Red Cell Transfusions

Chronic transfusion therapy prevents strokes in high-risk children (DeBaun, 2014). During pregnancy, the most dramatic benefit of prophylactic transfusions has been on maternal morbidity rates (Benites, 2016). In an observational 10-year prospective study at Parkland Hospital, we offered prophylactic transfusions to all pregnant women with sickle-cell syndromes. Transfusions were given throughout pregnancy to maintain the hematocrit above 25 volumes percent and the portion of hemoglobin S <60 percent (Cunningham, 1979). Maternal morbidity was minimal, and erythropoiesis suppression was not problematic. Their outcomes were compared with historical controls who were not routinely transfused. Overall, morbidity and hospitalization rates were significantly reduced in the transfused group (Asma, 2015; Cunningham, 1983; Grossetti, 2009). Still, adverse perinatal outcomes are prevalent (Ngô, 2010).

In a multicenter trial, Koshy and coworkers (1988) randomly assigned 72 pregnant women with sickle-cell syndromes to prophylactic or indicated transfusions. They reported a significant decline in the incidence of painful sickle-cell crises with prophylactic transfusions but no differences in perinatal outcomes. Because of risks inherent with blood administration, they concluded that prophylactic transfusions were not indicated. A metaanalysis of 12 studies found prophylactic transfusions improved rates of some adverse maternal and neonatal outcomes, including maternal mortality, pulmonary complications, and perinatal mortality (Malinowski, 2015).

Undoubtedly, morbidity from multiple transfusions is significant. Up to 10 percent of women had a delayed hemolytic transfusion reaction, and infections are major concerns. Garratty (1997) reviewed 12 studies and found alloimmunization developed in a fourth of women. Finally, in liver biopsies in these women, we found no evidence of transfusion-related iron overload, hemochromatosis, or chronic hepatitis (Yeomans, 1990).

Because of what some consider marginal benefits, routine prophylactic transfusions during pregnancy remain controversial (American College of Obstetricians and Gynecologists, 2015; Okusayna, 2013). Current consensus is that their use should be individualized.

#### Fetal Assessment

Because of the high incidence of fetal-growth restriction and perinatal mortality, serial fetal assessment with sonography and antepartum surveillance

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is recommended (American College of Obstetricians and Gynecologists, 2015). Anyaegbunam and colleagues (1991) reported nonreactive stress tests during sickling crises, which resumed reactivity with crisis resolution. They concluded that transient effects of sickle-cell crisis do not compromise umbilical blood flow.

### Labor and Delivery

Management is essentially identical to that for women with cardiac disease (Chap. 49, Labor and Delivery). Women should be kept comfortable, but not oversedated. Conduction analgesia is ideal (Camous, 2008). Compatible blood should be available. If a difficult vaginal or cesarean delivery is contemplated, and the hematocrit is <20 volumes percent, then packed erythrocyte transfusions are administered. There is no categorical contraindication to vaginal delivery, and cesarean delivery is reserved for obstetrical indications (Rogers, 2010).

### Contraception and Sterilization

Many clinicians do not recommend combination hormonal contraception because of potential adverse vascular and thrombotic effects. In their systematic review, however, Haddad and coworkers (2012) found that complication rates were not higher with their use in women with sickle-cell syndromes. The Centers for Disease Control and Prevention categorizes combination hormonal contraception, intrauterine devices, implants, and progestin-only contraception as having no risk or as having advantages that generally outweigh theoretical or proven risks (Curtis, 2016).

## Sickle-Cell Trait

The frequency of sickle-cell trait among African-Americans averages 8 percent. Carriers have occasional hematuria, renal papillary necrosis, and hyposthenuria, which is urine of low specific gravity (Tsaras, 2009). And although controversial, sickle-cell trait does not appear to be associated with increased rates of abortion, perinatal mortality, low birthweight, or pregnancy-induced hypertension (Pritchard, 1973; Tita, 2007; Tuck, 1983). One unquestioned relationship is the twofold increased incidence of asymptomatic bacteriuria and urinary infection. Sickle-cell trait should not be considered a deterrent to pregnancy or to hormonal contraception.

Inheritance is a concern for the fetus of a mother with sickle-cell trait whenever the father carries a gene for abnormal hemoglobins that include S, C, and D or for β-thalassemia trait. Prenatal diagnosis is discussed in Chapter 14 (Sickle Hemoglobinopathies).

## Hemoglobin C and C-β-Thalassemia

Approximately 2 percent of African-Americans are heterozygous for hemoglobin C, but even if homozygous, hemoglobin C is innocuous (Nagel, 2003). Only when coinherited with sickle-cell trait to yield hemoglobin SC is the trait problematic. Pregnancy in women with homozygous hemoglobin CC disease or C-β-thalassemia carries relatively benign associations. Table 56-3 shows our experiences from Parkland Hospital (Maberry, 1990). Other than mild-to-moderate anemia, pregnancy outcomes were not abnormal. Supplementation with folic acid and iron is indicated.

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TABLE 56-3

**Outcomes in 72 Pregnancies Complicated by Hemoglobin CC and C-β-Thalassemia**

| | Hemoglobin CC | C-β-Thalassemia |
|---|---|---|
| Women (no.) | 15 | 5 |
| Pregnancies (no.) | 49 | 23 |
| Hematocrit (range) | 27 (21–33) | 30 (28–33) |
| Birthweight (g) | | |
| Mean | 2990 | 2960 |
| Range | 1145–4770 | 2320–3980 |
| Perinatal deaths | 1 | 2 |
| Surviving infants | 42 | 20 |

Data from Maberry, 1990.

### Hemoglobin E

Although uncommon in the United States, hemoglobin E is the second most frequent hemoglobin variant worldwide. The heterozygous E trait is common in Southeast Asia. Hurst and coworkers (1983) identified homozygous hemoglobin E, hemoglobin E plus β-thalassemia, or hemoglobin E trait in 36 percent of Cambodians and 25 percent of Laotians. Hemoglobin EE is associated with little or no anemia, hypochromia, marked microcytosis, or erythrocyte targeting. Kemthong and colleagues (2016) studied 1073 women and 2146 controls and found that hemoglobin E trait does not increase pregnancy risks other than asymptomatic bacteriuria. Conversely, doubly heterozygous E-β-thalassemia is a common cause of severe childhood anemia in Southeast Asia (DeLoughery, 2014). In a cohort study of 54 women with singleton pregnancies, Luewan and associates (2009) reported a threefold greater risk of preterm birth and fetal-growth restriction in affected women. It is unclear if hemoglobin SE disease is ominous during pregnancy.

### Hemoglobinopathy in the Newborn

Neonates with homozygous SS, SC, and CC disease can be identified accurately at birth by cord blood electrophoresis. The United States Preventive Services Task Force recommends that all newborns be tested for sickle-cell disease (Lin, 2007). In most states, such screening is mandated by law and performed routinely (Chap. 32, Routine Newborn Care).

### Prenatal Diagnosis

Many tests are available to detect sickle-cell disease antenatally. Most are DNA based and use chorionic villus samples or amniotic fluid specimens (American College of Obstetricians and Gynecologists, 2015). Several mutations that encode hemoglobin S and other abnormal hemoglobins can be detected by targeted mutation analysis and polymerase chain reaction-based techniques (Chap. 13, Genetic Tests).

## THALASSEMIA SYNDROMES

Hundreds of mutations affect genes that control hemoglobin production. Some of these impair synthesis of one or more of the normal globin peptide

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chains and may result in a clinical syndrome characterized by varying degrees of ineffective erythropoiesis, hemolysis, and anemia (Benz, 2015). Thalassemias are classified according to the globin chain that is deficient. The two major forms involve impaired production or instability of α-peptide chains to cause α-thalassemia or of β-chains to cause β-thalassemia. These may form from point mutations, deletions, or translocations involving the α- or non-α-globin gene (Leung, 2012).

## Alpha Thalassemias

Because there are four α-globin genes, the inheritance of α-thalassemia is more complicated than for β-thalassemia (Piel, 2014). Possible genotypes and phenotypes are shown in Table 56-4. Clinical severity closely correlates with the degree of α-globin chains synthesis impairment. In most populations, the α-globin chain "cluster" or gene loci are doubled on chromosome 16. Similarly, the γ chains are duplicated. Thus, the normal genotype for diploid cells can be expressed as αα/αα and γγ/γγ. There are two main groups of α-thalassemia determinants: $\alpha^0$-thalassemia is the deletion of both loci from one chromosome

TABLE 56-4

**Genotypes and Phenotypes of α-Thalassemia Syndromes**

| Genotype | Genotype | Phenotype |
|---|---|---|
| Normal | αα/αα | Normal |
| $\alpha^+$-Thalassemia heterozygote | −α/αα<br>αα/−α | Normal; silent carrier |
| $\alpha^+$-Thalassemia homozygote[a]<br>$\alpha^0$-Thalassemia heterozygote[b] | −α/−α<br>−−/αα | α-Thalassemia minor—mild hypochromic microcytic anemia |
| Compound heterozygous $\alpha^0/\alpha^+$ | −−/−α | Hgb H ($\beta_4$) with moderate-to-severe hemolytic anemia |
| Homozygous α-thalassemia | −−/−− | Hgb Bart ($\gamma_4$) disease, hydrops fetalis |

[a]More common in African Americans.

[b]More common in Asian Americans.

(−−/αα), whereas $\alpha^+$-thalassemia is the loss of a single locus from one allele (−α/αα heterozygote) or a loss from each allele (−α/−α homozygote).

There are two major phenotypes. The deletion of all four α-globin chain genes (−−/−−) characterizes *homozygous* α-thalassemia. Because α-chains are contained in fetal hemoglobin, the fetus is affected. When none of the four genes are expressed, no α-globin chains are produced, and instead hemoglobin Bart ($\gamma_4$) and hemoglobin H ($\beta_4$) are formed as abnormal tetramers that cannot transport oxygen (Chap. 7, Hemopoiesis).

### Frequency

The relative frequency of α-thalassemia minor, hemoglobin H disease, and hemoglobin Bart disease varies remarkably among racial groups. All of these variants are encountered in Asians. In those of African descent, although α-thalassemia minor has a frequency approximating 2 percent, hemoglobin H disease is rare and hemoglobin Bart disease is unreported. This is because Asians usually have $\alpha^0$-thalassemia minor inherited with both gene deletions typically from the same chromosome (−−/αα), whereas blacks usually have $\alpha^+$-thalassemia minor in which one gene is deleted from each chromosome (−α/−α).

Diagnosis of β-thalassemia minor and α-thalassemia major in the fetus can be accomplished by DNA analysis using molecular techniques (Piel, 2014).

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Fetal diagnosis of hemoglobin Bart has been described using capillary electrophoresis or high-performance liquid chromatography techniques (Sirichotiyakul, 2009; Srivorakun, 2009). Molecular genetic testing for *HBA1* and *HBA2* identifies 90 percent of deletions and 10 percent of point mutations in affected individuals (Galanello, 2011b).

### Pregnancy

Important obstetrical aspects of some α-thalassemia syndromes depend on the number of gene deletions in a given woman. The silent carrier state with one gene deletion is of no consequence. Deletion of two genes resulting in *α*-thalassemia minor is characterized by minimal-to-moderate hypochromic microcytic anemia. This is due to either $\alpha^0$- or $\alpha^+$-thalassemia trait, and thus genotypes may be –α/–α or ––/αα. Differentiation is possible only by DNA analysis (Piel, 2014). Because no other clinical abnormalities accompany either form of α-thalassemia minor, it often goes unrecognized and is usually of no maternal consequence (Hanprasertpong, 2013). The fetus with these forms of thalassemia minor will have hemoglobin Bart at birth, but as its levels drop, it is not replaced by hemoglobin H. Red cells are hypochromic and microcytic, and the hemoglobin concentration is normal to slightly depressed.

*Hemoglobin H disease* ($\beta_4$) results from the compound heterozygous state for $\alpha^0$- plus $\alpha^+$-thalassemia with deletion of three of four alpha genes (––/–α). With only one functional α-globin gene per diploid genome, the newborn will have abnormal red cells containing a mixture of hemoglobin Bart ($\gamma_4$), hemoglobin H ($\beta_4$), and hemoglobin A. The neonate appears normal but soon develops hemolytic anemia as most of the hemoglobin Bart is replaced by hemoglobin H. In adults, anemia is moderate to severe and usually worsens during pregnancy.

Inheritance of all four abnormal α genes causes homozygous α-thalassemia with predominant production of hemoglobin Bart, which has an appreciably increased affinity for oxygen. This is incompatible with extended survival. Hsieh and colleagues (1989) reported that blood obtained by funipuncture from 20 hydropic fetuses contained 65 to 98 percent Bart hemoglobin. These fetuses are stillborn, or they are hydropic and usually die very soon after birth.

Sonographic measurement of the fetal cardiothoracic ratio at 12 to 13 weeks' gestation can be used to identify affected fetuses (Lam, 1999; Zhen, 2015). Sonographic assessment of myocardial performance—the *Tei index*—in the first half of pregnancy has been evaluated. Changes predate hydrops in affected fetuses (Luewan, 2013). Severe anemia can be detected using Doppler velocimetry of the middle cerebral artery. Hemopoietic cell transplantation has been described for treatment (Galanello, 2011a).

## Beta Thalassemias

The β-thalassemias are the consequences of impaired β-globin chain production or α-chain instability. Genes that encode control of β-globin synthesis are in the δγβ-gene "cluster" located on chromosome 11 (Chap. 7, Hemopoiesis). More than 150 point mutations in the β-globin gene have been described (Weatherall, 2010). In β-thalassemia, β-chain production is decreased, and excess α-chains precipitate to cause cell-membrane damage. Other forms of β-thalassemias are caused by α-chain instability (Kihm, 2002).

The heterozygous trait is β-thalassemia minor, and those most commonly encountered have elevated hemoglobin $A_2$ levels. This hemoglobin is composed of two α- and two δ-globin chains, and concentrations are usually more than 3.5 percent. Hemoglobin F—composed of two α- and two γ-globin chains—also usually has increased concentrations that exceed 2 percent. Some patients with heterozygous β-thalassemia minor do not have anemia, and others have mild-to-moderate anemia characterized by hypochromia and microcytosis.

Homozygous β-thalassemia—also called β-thalassemia major or *Cooley anemia*—is a serious and frequently fatal disorder. Hemolysis is intense and leads to severe anemia. Many patients become transfusion dependent, and the subsequent iron load, along with abnormally increased gastrointestinal iron absorption, leads to hemochromatosis, which is fatal in many cases. Stem cell transplantation has been used to treat β-thalassemia major (Jagannath, 2014). A heterozygous form of β-thalassemia that clinically manifests as *thalassemia intermedia* produces moderate anemia.

### Pregnancy

During pregnancy, women with β-thalassemia minor may have mild anemia (Charoenboon, 2016). Iron and folate supplements are given. In some women, anemia will worsen because normal plasma volume expansion may be accompanied by slightly subnormal erythropoiesis.

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Thalassemia major and some of the other severe forms were uncommonly encountered during pregnancy before the advent of transfusion and iron chelation therapy. With such management, 63 pregnancies were reported and suffered no serious complications (Aessopos, 1999; Daskalakis, 1998). Pregnancy is considered reasonably safe if maternal cardiac function is normal. Transfusions are given throughout pregnancy to maintain the hemoglobin concentration at 10 g/dL. This is coupled with surveillance of fetal growth (American College of Obstetricians and Gynecologists, 2015; Sheiner, 2004).

### Prenatal Diagnosis

Because β-thalassemia major is caused by numerous mutations, prenatal diagnosis is difficult. For a given individual, targeted mutation analysis is done that requires prior identification of the familial mutation. The analysis is done using chorionic villus sampling and other techniques discussed in Chapter 14 (Chorionic Villus Sampling). Noninvasive testing of circulating fetal nucleic acids in maternal plasma for the diagnosis of β-thalassemia has been described (Leung, 2012; Xiong, 2015).

## PLATELET DISORDERS

### Thrombocytopenia

Platelet abnormalities may precede pregnancy, develop during pregnancy coincidentally, or be induced by pregnancy. Thrombocytopenia—defined by a platelet count <150,000/μL—is identified in nearly 10 percent of gravidas (American College of Obstetricians and Gynecologists, 2016c). Of these cases, 75 percent are *gestational thrombocytopenia,* whereas 25 percent are due to other various causes. One other common cause is HELLP syndrome. Thrombocytopenia may be inherited or idiopathic, acute or chronic, and primary or associated with other disorders. Examples are shown in Table 56-5.

TABLE 56-5

**Some Causes of Thrombocytopenia in Pregnancy**

| |
|---|
| Gestational thrombocytopenia—75 percent |
| Preeclampsia and HELLP syndromes—20 percent |
| Obstetrical coagulopathies—DIC, MTP |
| Immune thrombocytopenic purpura |
| Systemic lupus erythematosus and APAS |
| Infections—viral and sepsis syndrome |
| Drugs |
| Hemolytic anemias |
| Thrombotic microangiopathies |
| Malignancies |

APAS = antiphospholipid antibody syndrome; DIC = disseminated intravascular coagulopathy; HELLP = hemolysis, elevated liver enzyme levels, low platelet count; MTP = massive transfusion protocol.

Data from American College of Obstetrics and Gynecologists, 2016c; Aster, 2007; Diz-Küçükkāya, 2016.

### Gestational Thrombocytopenia

Burrows and Kelton (1993) reported that 6.6 percent of 15,471 pregnant women had a platelet count <150,000/μL, and in 1.2 percent, it was <100,000/μL. They further noted that almost 75 percent of 1027 women whose platelet counts were <150,000/μL were found to have normal-variant incidental thrombocytopenia. Of the remainder, 21 percent had a hypertensive disorder of pregnancy, and 4 percent had an immunological disorder. A platelet count of <80,000/μL should trigger an evaluation for etiologies other than incidental or gestational thrombocytopenia, which is unlikely to have a

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platelet count <50,000/µL (Gernsheimer, 2013).

The physiological decline in platelet concentration seen with gestational thrombocytopenia is usually evident in the third trimester and is thought to be predominantly due to hemodilution. The normal increased splenic mass characteristic of pregnancy may also be contributory (Maymon, 2006). Most evidence shows that platelet life span is unchanged in normal pregnancy (Kenny, 2015).

### Inherited Thrombocytopenias

*Bernard-Soulier syndrome* is characterized by lack of platelet membrane glycoprotein (GPIb/IX) and causes severe dysfunction. Moreover, women exposed to fetal platelets carrying this glycoprotein can develop antibodies against this fetal GPIb/IX antigen to cause alloimmune fetal thrombocytopenia (Fujimori, 1999; Peng, 1991).

A systematic review of 30 pregnancies in 18 women reported a 33-percent rate of primary postpartum hemorrhage, and half of women with bleeding required blood transfusion (Peitsidis, 2010). The reviewers also described six cases of neonatal alloimmune thrombocytopenia and two perinatal deaths. Close monitoring throughout pregnancy and 6 weeks postpartum is critical due to the possibility of life-threatening hemorrhage (Prabu, 2006).

*May-Hegglin anomaly* is an autosomal dominant disorder characterized by thrombocytopenia, giant platelets, and leukocyte inclusions (Chatwani, 1992). Urato and Repke (1998) described such a woman who was delivered vaginally. Despite a platelet count of 16,000/µL, she did not bleed excessively. The neonate inherited the anomaly but also had no bleeding despite a platelet count of 35,000/µL. A systematic review of 26 studies containing 75 pregnancies in 40 women reported four cases of postpartum hemorrhage, 34 cases of neonatal thrombocytopenia, and two fetal deaths (Hussein, 2013).

### Immune Thrombocytopenic Purpura

The primary form—also termed *idiopathic thrombocytopenic purpura (ITP)*—is usually caused by a cluster of IgG antibodies directed against one or more platelet glycoproteins (Konkle, 2015). Antibody-coated platelets are destroyed prematurely in the reticuloendothelial system, especially the spleen. Although not proven, the disorder is probably mediated by autoantibodies directed at platelet-associated immunoglobulins—PAIgG, PAIgM, and PAIgA. In adults, immune thrombocytopenia most often is a chronic disease that rarely resolves spontaneously.

As shown in Table 56-5, secondary forms of immune-mediated chronic thrombocytopenia appear in association with systemic lupus erythematosus, lymphomas, leukemias, and several systemic diseases. Approximately 2 percent of thrombocytopenic patients have positive serological tests for lupus, and in some cases, levels of anticardiolipin antibodies are high. Finally, approximately 10 percent of HIV-positive patients have associated thrombocytopenia (Scaradavou, 2002).

#### Diagnosis and Management

Only a few adults with primary immune thrombocytopenia recover spontaneously, and for those who do not, platelet counts usually range from 10,000 to 100,000/µL (George, 2014). Evidence does not suggest that pregnancy increases the risk of relapse in women with previously diagnosed disease or worsens thrombocytopenia in women with active disease. That said, it is certainly not unusual for women who have been in clinical remission for several years to have recurrent thrombocytopenia during pregnancy. Although this may be from closer surveillance, hyperestrogenemia has also been implicated.

Therapy is considered if the platelet count is below 30,000 to 50,000/µL (American College of Obstetricians and Gynecologists, 2016c). Primary treatment includes corticosteroids or intravenous immune globulin (IVIG) (Neunert, 2011). Initially, prednisone, 1 mg/kg daily, is given to suppress the phagocytic activity of the splenic monocyte-macrophage system. IVIG given in a total dose of 2 g/kg during 2 to 5 days is also effective.

In pregnant women with no response to corticosteroid or IVIG therapy, open or laparoscopic splenectomy may be effective. In late pregnancy, cesarean delivery may be necessary for surgical exposure. Improvement usually follows splenectomy in 1 to 3 days and peaks at approximately 8 days. Cytotoxic agents are typically avoided in pregnancy due to teratogenicity risks. Azathioprine and rituximab, however, which are used in nonpregnant persons with ITP, have been used for other conditions in pregnancy. Finally, the thrombopoietin agonist *romiplostim* has stimulated responses in some patients (Decrooq, 2014; Imbach, 2011; Kuter, 2010).

#### Fetal and Neonatal Effects

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Pregnancy complications that are increased with ITP include stillbirth, fetal loss, and preterm birth (Wyszynski, 2016). Platelet-associated IgG antibodies cross the placenta, and fetal death from hemorrhage occurs occasionally (Webert, 2003). The severely thrombocytopenic fetus is at increased risk for intracranial hemorrhage with labor and delivery, but fortunately this is unusual. Payne and associates (1997) reviewed studies of maternal ITP published since 1973. Of 601 newborns, 12 percent had severe thrombocytopenia with counts <50,000/μL. Six infants had intracranial hemorrhage, and in three, their initial platelet count was >50,000/μL. This is consistent with a study of 127 pregnancies in women with ITP in which 10 to 15 percent of neonates had transient ITP (Koyama, 2012).

Investigators concur that fetal and maternal platelet counts lack strong correlation (George, 2009; Hachisuga, 2014). Because of this, maternal IgG free platelet antibody levels and platelet-associated antibody levels have been evaluated to predict fetal platelet counts. Again, however, there is little concurrence with these.

Investigators have also examined the association between the specific cause of thrombocytopenia and risk of a thrombocytopenic fetus. Four researched causes include gestational thrombocytopenia, hypertension-associated thrombocytopenia, immune thrombocytopenia, and alloimmune thrombocytopenia. Burrows and Kelton (1993) reported neonatal umbilical cord platelet counts measuring <50,000/μL in 19 of 15,932 consecutive newborns (0.12 percent). Only one of 756 mothers with gestational thrombocytopenia had an affected newborn. Of 1414 hypertensive women with thrombocytopenia, five neonates had thrombocytopenia. In contrast, of 46 mothers with immunological thrombocytopenia, four infants had thrombocytopenia. Alloimmune thrombocytopenia was associated with profound thrombocytopenia and cord platelet counts <20,000/μL. One of these fetuses died, and two others had intracranial hemorrhage.

#### Detection of Fetal Thrombocytopenia

Because no test accurately predicts fetal platelet counts, direct fetal blood sampling is necessary. Scott and coworkers (1983) obtained intrapartum scalp blood samples and recommended cesarean delivery for fetuses with platelet counts <50,000/μL. Daffos and colleagues (1985) reported that percutaneous umbilical cord blood sampling (PUBS) for this indication had a high complication rate (Chap. 14, Fetal Blood Sampling). Conversely, Berry and associates (1997) reported no complications and described poor reliability to predict severe thrombocytopenia, but noted a high negative-predictive value. Payne and coworkers (1997) summarized six studies in which fetal blood sampling was done for platelet estimation. Of the total of 195 fetuses, severe neonatal thrombocytopenia <50,000/μL was found in 7 percent. But, serious complications from cordocentesis were noted in 4.6 percent. Because of the low incidence of severe neonatal thrombocytopenia and morbidity, fetal platelet determinations and cesarean delivery are not recommended (Neunert, 2011).

#### Alloimmune Thrombocytopenia

Disparity between maternal and fetal platelet antigens can stimulate maternal production of antiplatelet antibodies. Such platelet alloimmunization can be severe, and its pathophysiology is identical to that caused by red cell antigens (Chap. 15, Fetal Thrombocytopenia).

### Thrombocytosis

Also called *thrombocythemia*, thrombocytosis generally is defined as persistent platelet counts >450,000/μL. Common causes of *secondary* or *reactive thrombocytosis* are iron deficiency, infection, inflammatory diseases, and malignant tumors (Deutsch, 2013). Platelet counts seldom exceed 800,000/μL in these secondary disorders, and prognosis depends on the underlying disease. On the other hand, *primary* or *essential thrombocytosis* accounts for most cases in which platelet counts exceed 1 million/μL. It is a clonal disorder frequently due to an acquired mutation in the *JAK2* gene (Konkle, 2015). Thrombocytosis usually is asymptomatic, but arterial and venous thromboses may develop, and thrombosis is associated with pregnancy complications (Rabinerson, 2007; Randi, 2014). These cases must be differentiated from the *sticky platelet syndrome,* which is also associated with thromboses (Rac, 2011).

Normal pregnancies have been described in women whose mean platelet counts were >1.25 million/μL (Beard, 1991; Randi, 1994). Others report more adverse outcomes. Niittyvuopio and associates (2004) described 40 pregnancies in 16 women with essential thrombocythemia. Almost half had a spontaneous abortion, fetal demise, or preeclampsia. In 63 pregnancies in 36 women cared for at the Mayo Clinic, a third had a spontaneous miscarriage, but other pregnancy complications were uncommon (Gangat, 2009). In this observational study, aspirin therapy was associated with a significantly lower abortion rate than that in untreated women—1 versus 75 percent, respectively.

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Suggested treatments during pregnancy include aspirin, low-molecular-weight heparin, and interferon-α (Finazzi, 2012). Interferon-α therapy during pregnancy was successful in 11 women in the review by Delage and coworkers (1996). One of these women had transient blindness at midpregnancy when her platelet count was 2.3 million/μL.

## Thrombotic Microangiopathies

Although not a primary platelet disorder, some degree of thrombocytopenia accompanies the thrombotic microangiopathies, which include *thrombotic thrombocytopenic purpura (TTP)* and *hemolytic uremic syndrome (HUS)*. These syndromes have an incidence of 2 to 6 per million persons per year (Miller, 2004). Their similarities to HELLP syndrome allude to their obstetrical ramifications (George, 2014).

### Etiopathogenesis

Although different causes account for the variable findings within these syndromes, clinically, they frequently are indistinguishable. Most cases of TTP are thought to be caused by antibodies to or a plasma deficiency of ADAMTS13 (Ganesan, 2011; Sadler, 2010). This endothelium-derived protease cleaves von Willebrand factor (vWF) to decrease its activity. Conversely, HUS is usually due to endothelial damage incited by viral or bacterial infections and is seen primarily in children (Ardissino, 2013; George, 2014).

With TTP, intravascular platelet aggregation stimulates a cascade of events leading to end-organ failure. There is endothelial activation and damage, but it is unclear whether this is a consequence or a cause. Elevated levels of unusually large multimers of vWF are identified with active TTP. Various defects in the *ADAMTS13* gene create differing clinical presentations of thrombotic microangiopathy (Camilleri, 2007; Moake, 2002, 2004). In another scheme, antibodies raised against ADAMTS13 neutralize its action to cleave vWF multimers during an acute episode. The end result is microthrombi of hyaline material consisting of platelets and small amounts of fibrin within arterioles and capillaries. When sufficient in number or size, these aggregates produce ischemia or infarctions in various organs.

### Clinical and Laboratory Manifestations

Thrombotic microangiopathies are characterized by thrombocytopenia, fragmentation hemolysis, and variable organ dysfunction. TTP is characterized by the pentad of thrombocytopenia, fever, neurological abnormalities, renal impairment, and hemolytic anemia. HUS typically has more profound renal involvement and fewer neurological aberrations.

Thrombocytopenia is usually severe, but fortunately, even with very low platelet counts, spontaneous severe hemorrhage is uncommon. Microangiopathic hemolysis is associated with moderate-to-marked anemia, and erythrocyte transfusions are frequently necessary. The blood smear is characterized by erythrocyte fragmentation with schizocytosis. Reticulocytes and nucleated red blood cells are increased, lactate dehydrogenase (LDH) levels are high, and haptoglobin concentrations are decreased. Consumptive coagulopathy, although common, is usually subtle and clinically insignificant.

### Treatment

The cornerstone of treatment is plasmapheresis with fresh-frozen plasma replacement. Plasma exchange removes inhibitors and replaces the ADAMTS13 enzyme (George, 2014; Michael, 2009). Treatment with caplacizumab, the anti-vWF immunoglobulin, inhibits the interaction between ultralarge vWF multimers and platelets (Peyandi, 2016).

These treatments have remarkably improved outcomes in patients with these formerly fatal syndromes. Red cell transfusions are imperative for life-threatening anemia. Treatment is usually continued until the platelet count is >150,000/μL. Unfortunately, relapses are common. Additionally, there may be long-term sequelae such as renal impairment (Dashe, 1998; Vesely, 2015). Treatment for pregnancy-associated HUS, which is complement mediated, uses the anti-C5 humanized monoclonal antibody eculizumab (Ardissino, 2013; Cañigral, 2014; Fakhouri, 2016).

### Pregnancy

As shown in the Appendix (Serum and Blood Constituents), ADAMTS13 enzyme activity decreases across pregnancy by up to 50 percent (Sánchez-Luceros, 2004). Levels drop even further with the preeclampsia syndrome. This is consonant with prevailing opinions that TTP is more commonly seen during pregnancy. The Parkland Hospital experiences were described by Dashe and coworkers (1998), who identified 11 pregnancies complicated by

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these syndromes among nearly 275,000 obstetrical patients—a frequency of 1 in 25,000.

It seems likely that some of the disparately higher incidence in pregnancy reported by others is because of inclusion of women with severe preeclampsia and eclampsia (Hsu, 1995; Magann, 1994). Differences that usually allow appropriate diagnosis are listed in Table 56-6. For example, moderate-to-severe hemolysis is a rather constant feature of thrombotic microangiopathies. But, this is seldom severe with the preeclampsia syndrome, even when complicated by HELLP syndrome (Chap. 40, Maternal Thrombocytopenia). And, although there is deposition of hyaline microthrombi within the liver with thrombotic microangiopathy, hepatocellular necrosis with elevated serum hepatic aminotransferase levels characteristic of preeclampsia is not a common feature (Ganesan, 2011; Sadler, 2010). Importantly, whereas delivery is imperative to reverse the preeclampsia syndrome, no evidence shows that thrombotic microangiopathy is improved by delivery (Dashe, 1998; Letsky, 2000). Finally, microangiopathic syndromes are usually recurrent and frequently unassociated with pregnancy. For example, seven of 11 women described by Dashe and colleagues (1998) had recurrent disease either when not pregnant or within the first trimester of a subsequent pregnancy. George (2009) reported recurrent TTP in only five of 36 subsequent pregnancies. That said, the risk for preeclampsia in these women is increased (Jiang, 2014).

TABLE 56-6

**Some Differential Factors between HELLP Syndrome and Thrombotic Microangiopathies**[a]

| | HELLP Syndrome | Thrombotic Microangiopathies |
|---|---|---|
| Thrombocytopenia | Mild/mod. | Mod./severe |
| Microangiopathic hemolysis (schizocytosis) | Mild | Severe |
| ADAMTS13 def. | Mild/mod. | Severe |
| DIC | Mild | Mild |
| Transaminitis (AST, ALT) | Mod./severe | None/mild |
| Treatment | Delivery | Plasmapheresis |

[a]Includes thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS).

ADAMTS13 = ADAM metallopeptidase with thrombospondin type 1 motif, 13; AST = aspartate transaminase; ALT = alanine transaminase; def. = deficiency; DIC = disseminated intravascular coagulopathy; HELLP = hemolysis, elevated liver enzyme levels, low platelet count; Mod. = moderate.

Unless the diagnosis is unequivocally one of these thrombotic microangiopathies, rather than severe preeclampsia, the response to pregnancy termination should be evaluated before resorting to plasmapheresis and exchange transfusion, massive-dose glucocorticoid therapy, or other therapy. Unfortunately, recall that determination of ADAMTS13 enzyme activity may be difficult to interpret with HELLP syndrome (Franchini, 2007). *Plasmapheresis is not indicated for preeclampsia-eclampsia complicated by hemolysis and thrombocytopenia.*

During the past two decades, and coincidental with plasmapheresis and plasma exchange, maternal survival rates from thrombotic microangiopathy have improved dramatically (Dashe, 1998). Although previously fatal in up to half of mothers, with such treatment, Egerman and coworkers (1996) reported two maternal and three fetal deaths in 11 pregnancies. Hunt and associates (2013) reported that TTP accounted for 1 percent of maternal deaths in the United Kingdom from 2003 to 2008.

### Long-Term Prognosis

Women who are diagnosed with thrombotic microangiopathy during pregnancy are at risk for serious long-term complications (Egerman, 1996). The Parkland experiences included a mean 9-year surveillance period (Dashe, 1998). These women had multiple recurrences; renal disease requiring dialysis, transplantation, or both; severe chronic hypertension; and transfusion-acquired infectious diseases. Two women died remote from

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pregnancy—one from dialysis complications and one from transfusion-acquired HIV infection.

In nonpregnant women who have recovered from thrombotic microangiopathies, persistent cognitive defects and physical disabilities have been reported (Kennedy, 2009; Lewis, 2009). Interestingly, as discussed in Chapter 40 (Renal Sequelae), these cognitive defects are very similar to those found in long-term surveillance studies of women who had eclampsia (Aukes, 2009, 2012; Wiegman, 2012).

## INHERITED COAGULATION DEFECTS

### Hemophilias A and B

Obstetrical hemorrhage may infrequently be the consequence of an inherited defect in a protein that controls coagulation. Both types of hemophilia are examples. Severity reflects plasma factor levels and is categorized as mild—levels of 6 to 30 percent; moderate—2 to 5 percent; or severe—less than 1 percent (Arruda, 2015).

*Hemophilia A* is an X-linked recessively transmitted disorder characterized by a marked deficiency of factor VIII. It is rare among women compared with men, in whom the heterozygous state is responsible for the disease. Heterozygous women have diminished factor VIII levels, but almost invariably, the homozygous state is requisite for hemophilia A. In a few instances, it appears in women spontaneously from a newly mutated gene. Pregnancy-associated acquired hemophilia A from antibodies may result in severe bleeding-related morbidity (Tengborn, 2012). *Christmas disease* or *hemophilia B* is caused by severe deficiency of factor IX and has similar genetic and clinical features.

#### Pregnancy

The risk of obstetrical bleeding with these is directly related to factor VIII or IX levels. Affected women have a range of activity that is determined by random X-chromosome inactivation—lyonization—although activity is expected to average 50 percent (Letsky, 2000). Levels below 10 to 20 percent pose hemorrhage risks. If levels fall to near zero, this risk is substantial. Pregnancy does afford some protection, however, because concentrations of both these clotting factors rise appreciably during normal pregnancy (Appendix, Serum and Blood Constituents). Treatment with desmopressin may also stimulate factor VIII release. Risks are further reduced by avoiding lacerations, minimizing episiotomy use, and maximizing postpartum uterine contractions. Operative vaginal deliveries should be avoided.

There are few published experiences during pregnancy. Kadir and coworkers (1997) reported that 20 percent of carriers had postpartum hemorrhage. Guy and associates (1992) reviewed five pregnancies in women with hemophilia B, and in all, outcomes were favorable. They recommended factor IX administration if levels are below 10 percent. Desmopressin has been shown in selected cases to reduce obstetrical bleeding complications (Trigg, 2012).

If a male fetus has hemophilia, the risk of hemorrhage increases after delivery in the neonate. This is especially true if circumcision is attempted.

#### Inheritance

If a mother has hemophilia A or B, all of her sons will have the disease, and all of her daughters will be carriers. If she is a carrier, half of her sons will inherit the disease, and half of her daughters will be carriers. Prenatal diagnosis of hemophilia is possible in some families using chorionic villus biopsy (Chap. 14, Chorionic Villus Sampling). Preimplantation genetic diagnosis for hemophilia was reviewed by Lavery (2009).

#### Factor VIII or IX Inhibitors

Rarely, antibodies directed against factor VIII or IX are acquired and may lead to life-threatening hemorrhage. Patients with hemophilia more commonly develop antibodies, and their acquisition in patients without hemophilia is extraordinary. It has been identified rarely in women during the puerperium (Santoro, 2009). The prominent clinical feature is severe, protracted, repetitive hemorrhage from the reproductive tract starting a week or so after an apparently uncomplicated delivery (Gibson, 2016). The activated partial thromboplastin time is markedly prolonged. Treatment has included multiple transfusions of blood component, immunosuppressive therapy, and attempts at various surgical procedures, especially curettage and hysterectomy. A recombinant activated factor VII (NovoSeven) stops bleeding in up to 75 percent of patients with these inhibitors (Arruda, 2015; Gibson, 2016).

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## Von Willebrand Disease

There are at least 20 heterogeneous clinical disorders involving aberrations of factor VIII complex and platelet dysfunction—collectively termed *von Willebrand disease (vWD).* These abnormalities are the most frequently inherited bleeding disorders, and their prevalence is as high as 1 to 2 percent (Arruda, 2015; Pacheco, 2010). Most von Willebrand variants are inherited as autosomal dominant traits, and types I and II are the most common. Specifically, type I accounts for 75 percent of von Willebrand variants. Type III, which is the most severe, is a recessive trait. Although most cases of acquired vWD develop after age 50 years, some have been reported in pregnant women (Lipkind, 2005).

### Pathogenesis

The *von Willebrand factor* is a series of large plasma multimeric glycoproteins that form part of the factor VIII complex. It is essential for normal platelet adhesion to subendothelial collagen and formation of a primary hemostatic plug. It also plays a major role in stabilizing the coagulant properties of factor VIII. The procoagulant component is factor VIII, a glycoprotein synthesized by the liver. Conversely, von Willebrand precursor, which is present in platelets and plasma, is synthesized by endothelium and megakaryocytes. The von Willebrand factor antigen (vWF:Ag) is the antigenic determinant measured by immunoassays.

### Clinical Presentation

Symptomatic patients typically present with easy bruising, epistaxis, mucosal hemorrhage, and excessive bleeding with trauma, including surgery. The classic autosomal dominant forms usually cause symptoms in the heterozygous state. With vWD, laboratory features often include a prolonged bleeding time, prolonged partial thromboplastin time, decreased vWF antigen levels, decreased factor VIII immunological and coagulation-promoting activity, and inability of platelets from an affected person to react to various stimuli.

### Pregnancy

During normal pregnancy, maternal levels of both factor VIII and vWF antigen increase substantively (Appendix, Serum and Blood Constituents). Because of this, pregnant women with vWD often develop normal levels of factor VIII coagulant activity and vWF antigen, although their measured bleeding time still may be prolonged. If factor VIII activity is very low or if there is bleeding, treatment is recommended. Desmopressin by infusion transiently increases factor VIII and vWF levels (Arruda, 2015; Kujovich, 2005). With significant bleeding, 15 or 20 units of cryoprecipitate are transfused every 12 hours. Alternatively, factor VIII concentrates (Alfanate, Hemate-P) may be given that contain high-molecular-weight vWF multimers. Lubetsky and colleagues (1999) described continuous infusion with Hemate-P in a woman during a vaginal delivery. According to Chi and coworkers (2009), conduction analgesia can be provided safely if coagulation defects have normalized or if hemostatic agents are administered prophylactically.

Pregnancy outcomes in women with vWD are generally good, but postpartum hemorrhage is encountered in up to half of cases. In a fourth of 38 cases summarized by Conti and associates (1986), bleeding was reported with abortion, with delivery, or in the puerperium. Kadir and coworkers (1998) reported their experiences with 84 pregnancies. They described a 20-percent incidence of immediate postpartum hemorrhage and another 20-percent incidence of late hemorrhage. Most cases were associated with low vWF levels in untreated women, and none given treatment peripartum had hemorrhage. More recently, Stoof and colleagues (2015) reviewed 185 deliveries in 154 affected women and found the risk for postpartum hemorrhage to be highest in deliveries with lowest factor levels.

### Inheritance

Although most patients with vWD have heterozygous variants and associated minor bleeding complications, the disease can be severe. Moreover, homozygous offspring develop serious clotting dysfunction. Chorionic villus sampling with DNA analysis to detect the missing genes has been described. Some authorities recommend cesarean delivery to avoid trauma to a possibly affected fetus if the mother has severe disease.

## Other Factor Deficiencies

In general, the activity of most procoagulant factors rises across pregnancy (Appendix, Serum and Blood Constituents). *Factor VII deficiency* is a rare autosomal recessive disorder. Levels of this factor normally increase during pregnancy, but these may rise only mildly in women with factor VII deficiency (Fadel, 1989). A systematic review of 94 births found no difference in postpartum hemorrhage rates with or without prophylaxis with recombinant factor VIIa (Baumann Kreuziger, 2013).

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*Factor X* or *Stuart-Prower factor* deficiency is rare and is inherited as an autosomal recessive trait. Factor X levels typically rise by 50 percent during normal pregnancy. Konje and colleagues (1994) described a woman who had 2-percent factor activity. She was given prophylactic treatment with plasma-derived factor X, which raised her plasma levels to 37 percent. Despite this, she suffered an intrapartum placental abruption. Bofill and coworkers (1996) gave intrapartum fresh-frozen plasma to a woman with less than 1-percent factor X activity. She delivered spontaneously without incident. Beksaç and associates (2010) described a woman with severe factor X deficiency who was successfully managed with prophylactic prothrombin complex concentrate. Nance and colleagues (2012) reported on 24 pregnancies, of which 18 resulted in a healthy baby.

*Factor XI—plasma thromboplastin antecedent—deficiency* is inherited as an autosomal trait. It manifests as severe disease in homozygotes but only as a minor defect in heterozygotes. It is most prevalent in Ashkenazi Jews and is rarely seen in pregnancy. Musclow and coworkers (1987) reported 41 deliveries in 17 affected women, and none required transfusion. In 105 pregnancies from 33 affected women, Myers and colleagues (2007) reported an uneventful pregnancy and delivery in 70 percent. They recommended peripartum treatment with factor XI concentrate if cesarean delivery is performed and advised against epidural analgesia unless factor XI is given. From their review, Martin-Salces and associates (2010) found that factor XI levels and bleeding severity correlated poorly in women with severe deficiency. Wiewel-Verschueren and colleagues (2015) performed a systematic review of 27 studies with 372 women and reported that 18 percent had postpartum hemorrhage.

*Factor XII deficiency* is another autosomal recessive disorder that rarely complicates pregnancy. A greater incidence of thromboembolism is encountered in nonpregnant patients with this deficiency. Lao and coworkers (1991) reported an affected pregnant woman in whom placental abruption developed at 26 weeks' gestation.

*Factor XIII deficiency* is an autosomal recessive trait and may be associated with maternal intracranial hemorrhage (Letsky, 2000). In their review, Kadir and associates (2009) cited an increased risk of recurrent miscarriage and placental abruption. It has also been reported to cause umbilical cord bleeding (Odame, 2014). Treatment is fresh frozen plasma. Naderi and colleagues (2012) described 17 successful pregnancies in women receiving weekly prophylaxis with Factor XIII concentrate.

Fibrinogen abnormalities—either qualitative or quantitative—also may cause coagulation abnormalities. Autosomally inherited abnormalities usually involve the formation of a functionally defective fibrinogen—commonly referred to as *dysfibrinogenemia* (Edwards, 2000). Familial *hypofibrinogenemia* and sometimes *afibrinogenemia* are infrequent recessive disorders. In some cases, both are found—*hypodysfibrinogenemia* (Deering, 2003). Our experience suggests that hypofibrinogenemia represents a heterozygous autosomal dominant state. The thrombin-clottable protein level in these patients typically ranges from 80 to 110 mg/dL when nonpregnant, and this increases by 40 or 50 percent in normal pregnancy. Those pregnancy complications that give rise to acquired hypofibrinogenemia, such as placental abruption, are more common with fibrinogen deficiency. Trehan and Fergusson (1991) and Funai and coworkers (1997) described successful outcomes in two affected women in whom fibrinogen or plasma infusions were given throughout pregnancy.

### Conduction Analgesia with Bleeding Disorders

Most serious bleeding disorders would logically preclude the use of epidural or spinal analgesia for labor or delivery. If the bleeding disorder is controlled, however, conduction analgesia may be considered. Chi and colleagues (2009) reviewed intrapartum outcomes in 80 pregnancies in 63 women with an inherited bleeding disorder. These included those with factor XI deficiency, hemophilia carrier status, vWD, platelet disorders, or a deficiency of factor VII, XI, or X. Regional block was used in 41. Of these, 35 had spontaneously normalized hemostatic dysfunction, and others were given prophylactic replacement therapy. The reviewers reported no unusual complications. Singh and associates (2009) reviewed 13 women with factor XI deficiency. Nine received neuraxial analgesia without complications, but only after fresh-frozen plasma was transfused to most to correct the activated partial thromboplastin time.

## THROMBOPHILIAS

Several important regulatory proteins act as inhibitors at strategic sites in the coagulation cascade to maintain blood fluidity. Inherited deficiencies of these inhibitory proteins are caused by gene mutations. Because they may be associated with recurrent thromboembolism, they are collectively referred to as *thrombophilias.* These are discussed in Chapter 52 (Thrombophilias) and reviewed by the American College of Obstetricians and Gynecologists (2017b).

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