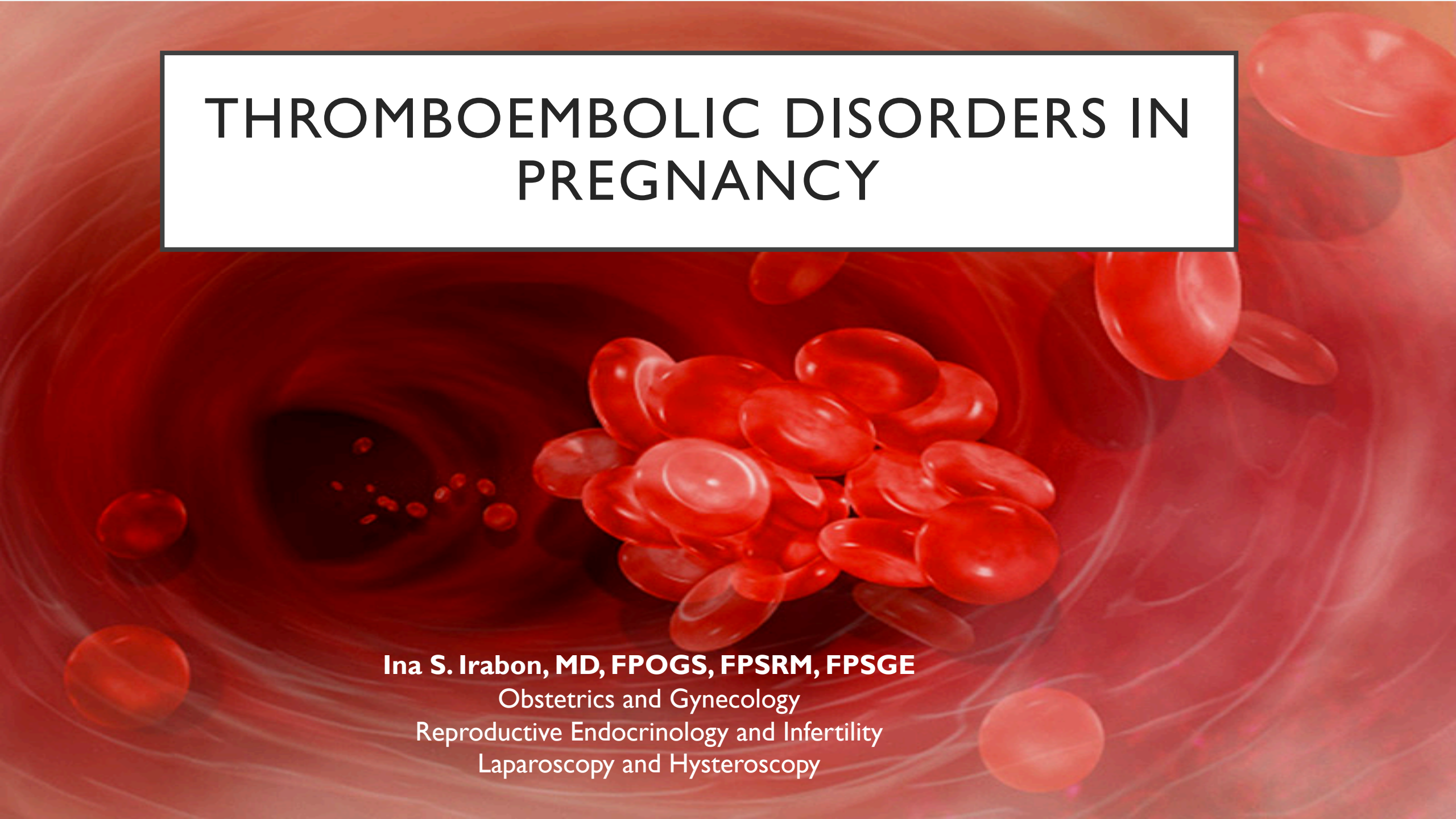
THROMBOEMBOLIC DISORDERS IN PREGNANCY



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OUTLINE

- PATHOPHYSIOLOGY
- THROMBOPHILIAS
- THROMBOPHILIA SCREENING
- DEEP-VEIN THROMBOSIS
- LABORANDDELIVERY
- SUPERFICIAL VENOUS THROMBOPHLEBITIS
- PULMONARYEMBOLISM
- THROMBOPROPHYLAXIS

VENOUS THROMBOSIS

- stasis, local trauma to the vessel wall, and hypercoagulability predispose to venous thrombosis development (Virchow's triad)
- Pregnancy: higher risk due to -
  - a. compression of great vessels
  - b. venous stasis and delivery → endothelial cell injury
  - c. increase in production of clotting factors

RISK FACTORS IN PREGNANCY

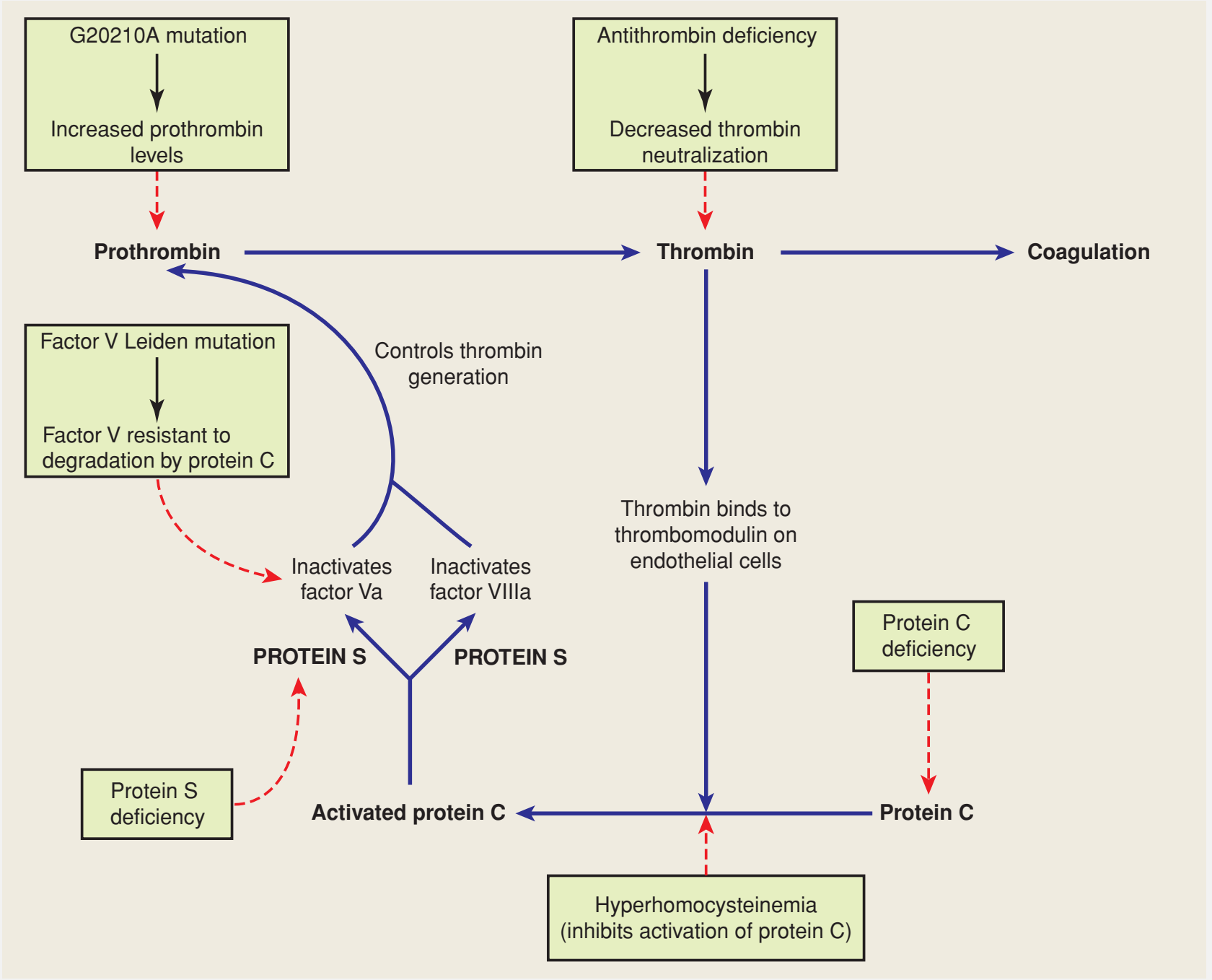
OBSTETRICAL

Cesarean delivery
Diabetes
Hemorrhage and anemia Hyperemesis
Immobility—prolonged bed rest
Multifetal gestation
Multiparity
Preeclampsia
Puerperal infection

GENERAL

Age 35 years or older
Cancer
Connective-tissue disease
Dehydration
Immobility—long-distance travel
Infection and inflammatory disease
Myeloproliferative disease
Nephrotic syndrome
Obesity
Oral contraceptive use
Orthopedic surgery
Paraplegia
Prior thromboembolism
Sickle-cell disease
Smoking
Thrombophilia

THROMBOPHILIAS


G20210A mutation
Increased prothrombin levels
Antithrombin deficiency
Decreased thrombin neutralization
Prothrombin
Thrombin
Coagulation
Factor V Leiden mutation
Factor V resistant to degradation by protein C
Controls thrombin generation
Thrombin binds to thrombomodulin on endothelial cells
Inactivates factor Va
Inactivates factor VIIIa
PROTEIN S
PROTEIN S
Protein C deficiency
Protein S deficiency
Activated protein C
Protein C
Hyperhomocysteinemia (inhibits activation of protein C)

INHERITED THROMBOPHILIA:

- Patients with inherited thrombophilic disorders often have a family history of thrombosis.
- also found in patients who present with:
  - venous thromboembolism before the age of 45 years, especially in the absence of well- recognized risk factors, such as surgery or immobilization
  - venous thromboembolism with minimal provocation such as after a long-distance flight or after taking estrogens.
  - family history of sudden death due to pulmonary embolism or a history of multiple family members requiring long-term anticoagulation therapy because of recurrent thrombosis

INHERITED THROMBOPHILIA:

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Activated Protein C Resistance—Factor V Leiden Mutation
- Prothrombin G20210A Mutation
- Hyperhomocysteinemia
- Other Thrombophilia Mutations

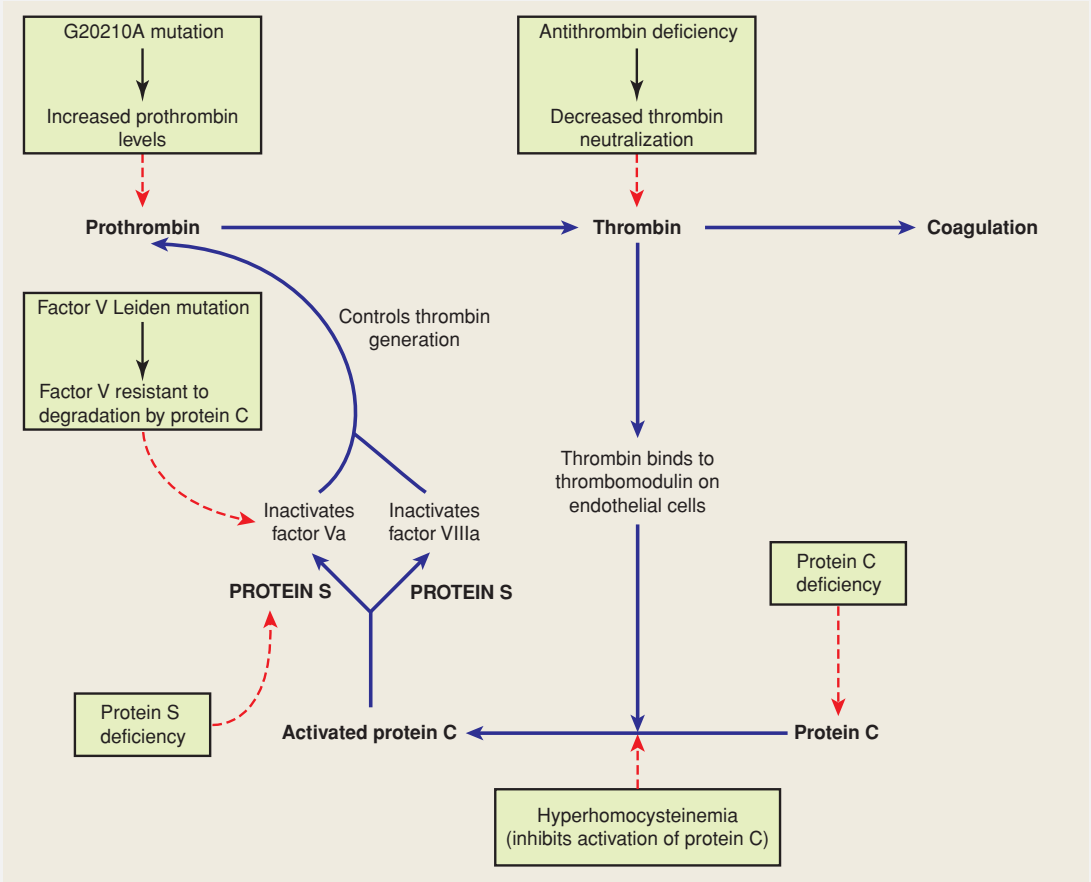


FIGURE 52-1 Overview of the inherited thrombophilias and their effect(s) on the coagulation cascade. (Adapted from Seligsohn, 2001.)

1. ANTITHROMBIN DEFICIENCY

- Antithrombin functions as a natural anticoagulant by binding and inactivating thrombin and the activated coagulation factors IXa, Xa, XIa, and XIIa
- Of note, the rate of antithrombin interaction with its target proteases is accelerated by heparin
- Antithrombin deficiency may result from hundreds of different mutations that are almost always autosomal dominant. Type I deficiency is the result of reduced synthesis of biologically normal antithrombin, and type II deficiency is characterized by normal levels of antithrombin with reduced functional activity

1. ANTITHROMBIN DEFICIENCY

- Antithrombin de ciency is rare, and it is the most thrombogenic of the heritable coagulopathies.
- thrombosis risk during pregnancy among antithrombin-deficient women without a personal or family history is 3 to 7 percent, and it is 11 to 40 percent with such a history

ANTITHROMBIN DEFICIENCY

- affected women are treated during pregnancy with heparin regardless of whether they have had a prior thrombosis.
- successful use of antithrombin concentrate infusions plus therapeutic anticoagulation in a pregnant woman with antithrombin deficiency who developed a thrombosis during the third trimester despite therapeutic doses of low-molecular-weight heparin.

PROTEIN C DEFICIENCY

- When thrombin is bound to thrombomodulin on endothelial cells of small vessels, its procoagulant activities are neutralized → this binding also activates protein C, a natural anticoagulant that in the presence of protein S controls thrombin generation, in part, by inactivating factors Va and VIIIa
- Activated protein C also inhibits the synthesis of plasminogen- activator inhibitor 1
- More than 100 different autosomal dominant mutations for the protein C gene have been described; prevalence of protein C deficiency is 2 to 3 per 1000, but many of these individ- uals do not have a thrombosis history because the phenotypic expression is highly variable

PROTEIN S DEFICIENCY

- this circulating anticoagulant is activated by protein C, which enhances its capacity to inactiviate factors Va and VIIIa
- Protein S deficiency may be caused by more than 100 different mutations, with prevalence of 2 per 1000
- Protein S deficiency may be measured by antigenically determined free, functional, and total S levels. All three decline substantively during normal gestation, thus the diagnosis in pregnant women—as well as in those taking certain oral contraceptives—is difficult
- If screening during pregnancy is necessary, threshold values for free protein S antigen levels in the second and third trimesters have been identified at less than 30 percent and less than 24 percent, respectively.
- Among those with a positive family history, the venous thromboembolism risk in pregnancy has been reported to be 6 to 7 percent (American College of Obstetricians and Gynecologists, 2013).
- Neonatal homozygous protein C or S deficiency is usually associated with a severe clinical phenotype known as **purpura fulminans** → characterized by extensive thromboses in the microcirculation soon after birth leading to skin necrosis

ACTIVATED PROTEIN C RESISTANCE—FACTOR V LEIDEN MUTATION

- e most prevalent of the known thrombophilia syndromes, this condition is characterized by resistance of plasma to the anticoagulant e ects of activated protein C. A number of muta- tions have been described, but the most common is the factor V Leiden mutation, which was named after the city in which it was described. is missense mutation in the factor V gene results from a substitution of glutamine for arginine at position 506 in the factor V polypeptide, which gains resistance to deg- radation by activated protein C. e unimpeded abnormal fac- tor V protein retains its procoagulant activity and predisposes to thrombosis (see Fig. 52-1).
- Heterozygous inheritance for factor V Leiden is the most common heritable thrombophilia. It is found in 3 to 15 per- cent of select European populations and 3 percent of African Americans, but it is virtually absent in African blacks and Asians (Lockwood, 2012). As shown in Table 52-2, women who are heterozygous for factor V Leiden account for approximately 40 percent of venous thromboembolism cases during pregnancy. However, the actual risk among pregnant women who are het- erozygous and who do not have a personal history or a rst-degree relative with a thrombotic episode before age 50 years is 5 to 12 per 1000. In contrast, this risk increases to at least 10 percent among women with a personal or family history. Pregnant women who are homozygous without a personal or family history have a 1- to 4-percent risk for venous thrombo- embolism, whereas those with such a history have an approxi- mately 17-percent risk (American College of Obstetricians and Gynecologists, 2013).
- As described later (p. 1034), diagnosis during pregnancy is performed by DNA analysis for the mutant factor V gene. is is because bioassay is confounded by the fact that resis- tance is normally increased after early pregnancy because of alterations in other coagulation proteins (Walker, 1997). Of note, activated protein C resistance can also be caused by antiphospholipid syndrome, which is described later (p. 1033) and also detailed in Chapter 59 (p. 1173) (Eldor, 2001; Saenz, 2011).
- To assess the prognostic signi cance of maternal factor V Leiden mutation during pregnancy, Kjellberg and colleagues (2010) compared the outcomes of 491 carriers with 1055 con- trols. All three of the thromboembolic events occurred among the carriers. But, there were no di erences in preterm birth, birthweight, or hypertensive complications between the two groups. Similarly, Hammerová and coworkers (2011) found that adverse pregnancy events were not increased among women with heterozygous mutations. In a meticulously exe- cuted prospective observational study of approximately 5000 women conducted by the Maternal-Fetal Medicine Units Network, Dizon-Townson and associates (2005) found that the heterozygous mutant gene incidence was 2.7 percent. Of three pulmonary emboli and one deep-vein thrombosis cases—a rate of 0.8 per 1000 pregnancies—none were among these carriers. ere was no increased risk of preeclampsia, placental abruption, fetal-growth restriction, or pregnancy loss in heterozygous women. e investigators concluded that universal prenatal screening for the Leiden mutation and prophylaxis for carriers without a prior venous thromboem- bolism is not indicated. Finally, Clark and colleagues (2002) concluded that such routine prenatal screening was not cost e ective.

PROTHROMBIN G20210A MUTATION

- is missense mutation in the prothrombin gene leads to excessive accumulation of prothrombin, which then may be converted to thrombin. As with factor V Leiden, a personal history or a family history of venous thromboembolism in a rst-degree relative before age 50 years increases the risk of venous thromboembolism during pregnancy (see Table 52-2). For a heterozygous carrier with such a history, the risk exceeds 10 percent. Without such a history, heterozygous carriers of the mutation have less than a 1-percent risk of venous thromboem- bolism during pregnancy (American College of Obstetricians and Gynecologists, 2013).
- Homozygous patients or those who coinherit a G20210A mutation with a factor V Leiden mutation have an even greater thromboembolism risk. Stefano and associates (1999) performed a retrospective cohort study of 624 nonpregnant patients with one prior episode of deep-vein thrombosis. ey found that those doubly heterozygous individuals had a 2.6- fold increased risk of recurrence relative to those with the het- erozygous Leiden mutation alone. ey concluded that carriers with both mutations are candidates for lifelong anticoagulation after a rst thrombotic episode.
- In a secondary analysis of the Maternal-Fetal Medicine Units Network study described earlier, Silver and cowork- ers (2010) tested nearly 4200 women for the prothrombin G20210A mutation. A total of 157—or 3.8 percent—of the women carried the mutation, and only one of these was homo- zygous. Carriers had similar rates of pregnancy loss, preeclamp- sia, growth restriction, and placental abruption compared with noncarriers. e three thromboembolic events occurred in women who tested negative for the mutation.

HYPERHOMOCYSTEINEMIA

- e most common cause of elevated homocysteine is the C667T thermolabile mutation of the enzyme 5, 10-methylene-tetrahydrofolate reductase (MTHFR). Inheritance is auto- somal recessive. Elevated homocysteine levels may also result from de ciency of one of several enzymes involved in methio- nine metabolism and from correctible nutritional de cien- cies of folic acid, vitamin B6, or vitamin B12 (Hague, 2003; McDonald, 2001). During normal pregnancy, mean homo-
- cysteine plasma concentrations are decreased (López-Quesada, 2003; McDonald, 2001). us, to make a diagnosis during pregnancy, Lockwood (2002) recommends a fasting threshold of > 12 μmol/L to de ne hyperhomocysteinemia.
- Although hyperhomocysteinemia was previously reported to be a modest risk factor for venous thromboembolism, more recent data indicate that an elevated homocysteine level is actually a weak risk factor (American College of Obstetricians and Gynecologists, 2013). In an interesting metaanalysis, den Heijer and colleagues (2005) found that international stud- ies of MTHFR polymorphisms were collectively associated with slightly increased signi cant risks for thrombosis—odds ratios 1.15 to 1.6. In contrast, studies conducted in North America collectively demonstrated no such association. e authors speculated that folic acid supplementation could explain the di erence. Recall that folic acid serves as a cofactor in the remethylation reaction of homocysteine to methionine. Similarly, the American College of Chest Physicians concluded that the lack of an association with thromboembolism could re ect the physiological reductions in homocysteine levels asso- ciated with pregnancy and the e ects of widespread prenatal folic acid supplementation (Bates, 2012).
- In a follow-up study of 167 women who developed a venous thromboembolism during pregnancy and 128 controls, Kovac and associates (2010) found no di erence in the prevalence of MTHFR C677T homozygosity between the two groups. e American College of Obstetricians and Gynecologists (2013) has concluded that there is insu cient evidence to support assessment of MTHFR polymorphisms or measurement of fasting homocys- teine levels in the evaluation for venous thromboembolism.

OTHER THROMBOPHILIA MUTATIONS

- A number of potentially thrombophilic polymorphisms are being discovered at an ever-increasing rate. Unfortunately, information regarding the prognostic signi cance of such newly discovered mutations is limited. For example, protein Z is a vitamin K-dependent protein that serves as a cofactor in factor Xa inactivation. Studies in nonpregnant patients have found that low protein Z levels are associated with an increased thromboembolism risk (Santacroce, 2006). Similarly, plasmin- ogen activator inhibitor type 1 (PAI-1) is an important regula- tor of brinolysis. Certain polymorphisms in the gene promoter have been associated with small increased venous thromboem- bolism risks. ese thrombophilias and others, including alter- native mutations in the factor V gene and activity-enhancing mutations in various clotting factor genes, appear to exert little independent risk for venous thromboembolism. And although they may exacerbate risk among patients when coinherited with other thrombophilias, the American College of Obstetricians and Gynecologists (2013) has concluded that there is insuf- cient evidence to recommend screening.
- As an interesting aside, Galanaud and coworkers (2010) hypothesized that a paternal thrombophilia could increase the risk of a maternal thromboembolism. Speci cally, these inves- tigators found that a paternal thrombophilia—the PROCR 6936G allele—a ects the endothelial protein C receptor. is receptor is expressed by villous trophoblast and thus is exposed to maternal blood. Although this research is preliminary, it could help explain the pathogenesis of recurrent idiopathic thromboses in pregnant women.

ACQUIRED THROMBOPHILIAS

- antiphospholipid syndrome
- heparin-induced thrombocytopenia
- cancer

ANTIPHOSPHOLIPID SYNDROME

- This prothrombotic disorder can affect both the venous and arterial circulations.
- The deeper veins of the lower limbs and the cerebral arterial circulation are the most frequent sites of venous and arterial thrombosis, respectively
- Besides thrombosis, the other major clinical manifestations of the APS are obstetrical
- Criteria include:
  - (1) at least one otherwise unexplained fetal death at or beyond 10 weeks;
  - (2) at least one preterm birth before 34 weeks' gestation because of eclampsia, severe preeclampsia, or placental insufficiency; or
  - (3) at least three unexplained consecutive spontaneous abortions before 10 weeks.

ANTIPHOSPHOLIPID SYNDROME

- Once one of the above clinical criteria—thrombosis or obstetrical—is met, antiphospholipid antibody testing should be performed to diagnose APS. These patients should be tested for the presence of three factors: (1) lupus anticoagulant, (2) anticardiolipin immunoglobulin G and M (IgG and IgM) antibodies, and (3) anti-β2-glycoprotein I IgG and IgM antibodies.
- If any of these laboratory test results are positive, a confirmatory test is performed 12 weeks later
- anticardiolipin antibody is the most common sole antiphospholipid antibody present;
- anti-β2-glycoprotein I is associated with the lowest live birth rate and highest incidences of preeclampsia, fetal-growth restriction, and stillbirth compared with anticardiolipin antibodies or lupus anticoagulant alone.
- These investigators also observed that despite therapy with low-dose aspirin and prophylactic LMWH heparin, the chance of a liveborn neonate was only 30 percent for women with positive test results for all three antibodies.
- The thrombosis risk rises significantly during pregnancy in women with APS. Indeed, up to 25 percent of thrombotic events in women with APS occur during pregnancy or in the puerperium. Looking at this a different way, women with APS have a 5- to 12-percent risk of thrombosis during pregnancy or the puerperium (American College of Obstetricians and Gynecologists, 2017a). This syndrome is discussed in more detail in Chapter 59 (p. 1143).

THROMBOPHILIAS AND PREGNANCY COMPLICATIONS

- Attention has been directed toward possible relationships between inherited thrombophilias and pregnancy complications other than thromboses. Summarized in Table 52-3 are the findings of 25 studies systematically reviewed by Robertson and associates (2005) and incorporated into the recommendations of the American College of Chest Physicians (Bates, 2012). Importantly, the considerable heterogeneity and wide confidence intervals illustrate the uncertainty of these associations.

THROMBOPHILIAS AND PREGNANCY COMPLICATIONS

- Other investigations underscore the heterogeneity of results. For example, Kahn and coworkers (2009) found no higher risk for early-onset or severe preeclampsia in women with factor V Leiden mutation, prothrombin G20210A mutation, MTHFR C677T polymorphism, or hyperhomocysteinemia. Said and associates (2010a) prospectively screened more than 2000 healthy nulliparous women for factor V Leiden, prothrombin gene mutation, MTHFR C677T, MTHFR A1298C, and thrombomodulin polymorphism. Women who carried the prothrombin gene mutation had a 3.6-fold greater risk of adverse pregnancy outcome, including severe preeclampsia, fetal-growth restriction, placental abruption, or stillbirth. But, none of the other polymorphisms conferred an elevated risk of these adverse outcomes. From the Stillbirth Collaborative Research Network, Silver and associates (2016) found a weak association between maternal factor V Leiden and stillbirth. There was no association between stillbirth and the other inherited thrombophilias. Based on their prospective study of 750 pregnancies complicated by stillbirth, Korteweg and colleagues (2010) concluded that routine thrombophilia testing after fetal death is inadvisable.
- The American College of Obstetricians and Gynecologists (2017c) notes that a definitive causal link cannot be made between inherited thrombophilias and adverse pregnancy outcomes. Moreover, in one randomized trial, Rodger and associates (2014) found that antepartum prophylactic LMWH did not reduce a composite outcome of pregnancy loss, severe or early-onset preeclampsia, small- for-gestational age neonates, and VTE in thrombophilic women.
- Thus, because of uncertainties in the magnitude of risk and in the benefits of prophylaxis given to prevent pregnancy complications in women with heritable thrombophilias, it remains unproven that universal screening is indicated (Louis- Jacques, 2016). In contrast, the association between APS and adverse pregnancy outcomes—including fetal loss, recurrent pregnancy loss, and preeclampsia—is much stronger.

THROMBOPHILIA SCREENING

- Given the relatively high incidence of thrombophilia in the population and the low incidence of VTE, universal screening during pregnancy is not cost effective (Carbone, 2010). Thus, a selective screening strategy is required. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend that thrombophilia screening be considered in the following clinical circumstances: (1) a personal history of VTE that was associated with a nonrecurrent risk factor such as fractures, surgery, and/or prolonged immobilization; and (2) a first-degree relative (parent or sibling) with a history of high-risk thrombophilia or VTE before age 50 years in the absence of other risk factors.
- The American College of Obstetricians and Gynecologists (2017c) notes that testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption is not recommended because clinical evidence that antepartum heparin prophylaxis prevents recurrence is insufficient. Similarly, testing is not recommended for women with a history of fetal-growth restriction or preeclampsia. The American College of Chest Physicians also recommends against screening women with prior pregnancy complications (Bates, 2012). However, screening for antiphospholipid antibodies may be appropriate in women who have experienced a fetal loss or early-onset preeclampsia (Berks, 2015).
- Methods of screening for the more common inherited thrombophilias are shown in Table 52-4. Whenever possible, laboratory testing is performed at least 6 weeks after the thrombotic event, while the patient is not pregnant, and when she is not receiving anticoagulation or hormonal therapy. Screening for hyperhomocysteinemia is not recommended (American College of Obstetricians and Gynecologists, 2017c).

HOW TO TEST FOR THROMBOPHILIA

Thrombophilia	Testing Method	Is Testing Reliable During Pregnancy?	Is Testing Reliable During Acute Thrombosis?	Is Testing Reliable with Anticoagulation?
Factor V Leiden mutation	Activated protein C resistance	Yes	Yes	No
	assay (second generation)	Yes	Yes	Yes
	If abnormal: DNA analysis			
Prothrombin gene mutation G20210A	DNA analysis	Yes	Yes	Yes
Protein C deficiency	Protein C activity (<60%)	Yes	No	No
Protein S deficiency	Functional assay (<55%)	No[a]	No	No
Antithrombin deficiency	Antithrombin activity (<60%)	Yes	No	No

[a]If screening in pregnancy is necessary, cutoff values for free protein S antigen levels in the second and third trimesters have been identified at less than 30% and less than 24%, respectively.

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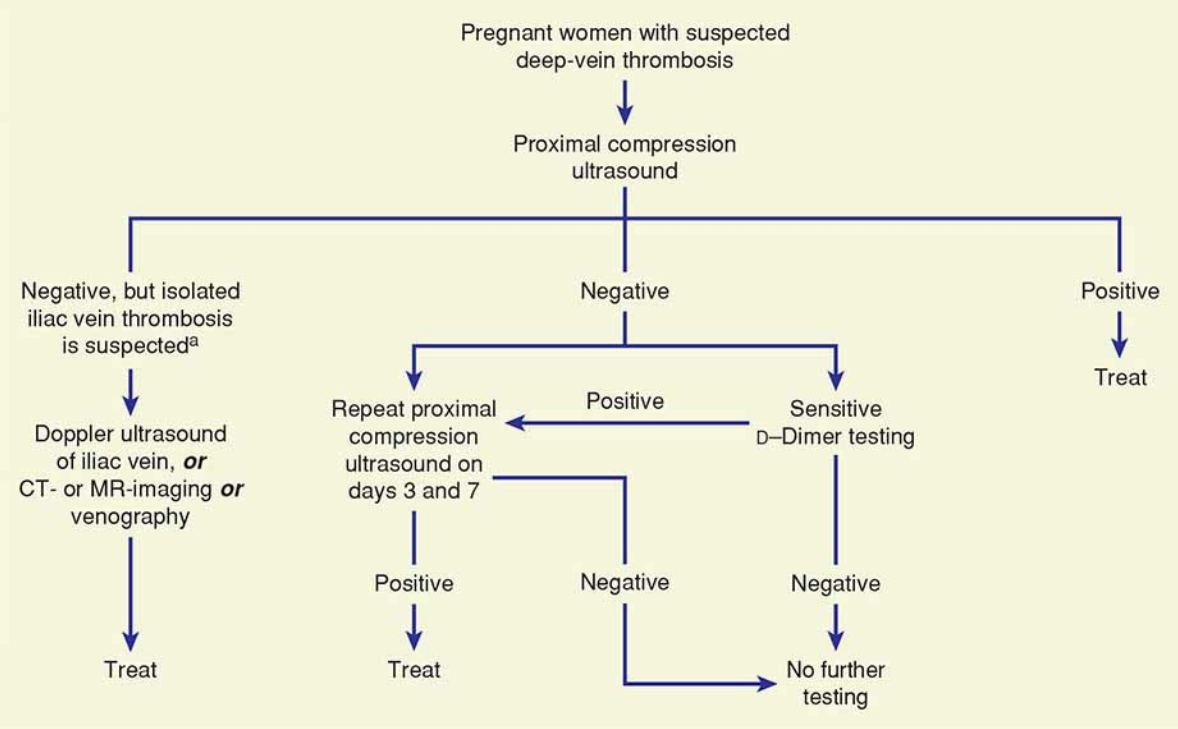
DEEP VEIN THROMBOSIS

- Clinical Presentation
- During pregnancy, most venous thromboses are confined to the deep veins of the lower extremity. Approximately 70 percent of cases are located in the iliofemoral veins without involvement of the calf veins. Isolated iliac vein and calf vein thromboses occur in approximately 17 and 6 percent of cases, respectively (Chan, 2010). In contrast, in the general population, more than 80 percent of deep-vein thromboses involve calf veins, and iliofemoral or isolated iliac vein thromboses are uncommon (Huisman, 2015).
- The signs and symptoms vary greatly and depend on the degree of occlusion and the intensity of the inflammatory response. Ginsberg and coworkers (1992) reported that 58 of 60 antepartum women—97 percent—had left leg thromboses. Blanco-Molina and coworkers (2007) reported left-leg involvement in 78 percent. Greer (2003) hypothesizes that this results from compression of the left iliac vein by the right iliac and ovarian artery, both of which cross the vein only on the left side. Yet, as described in Chapter 53 (p. 1026), the ureter is compressed more on the right side.
- Classically, thrombosis involving the lower extremity is abrupt in onset, and there is pain and edema of the leg and thigh. The thrombus typically involves much of the deep-venous system to the iliofemoral region. Occasionally, reflex arterial spasm causes a pale, cool extremity with diminished pulsations. Alternatively, there may be appreciable clot, yet little pain, heat, or swelling. Importantly, calf pain, either spontaneous or in response to squeezing or to Achilles tendon stretching—Homans sign—may be caused by a strained muscle or contusion. Between 30 and 60 percent of women with a confirmed lower-extremity acute deep-vein thrombosis have an asymptomatic pulmonary embolism (p. 1016

DEEP VEIN THROMBOSIS

- Diagnosis
- Clinical diagnosis of deep-vein thrombosis is difficult, and in an earlier study of pregnant women, the clinical diagnosis was confirmed in only 10 percent (Hull, 1990). Another challenge is that many of the common diagnostic tests that have been investigated extensively in nonpregnant patients have not been validated appropriately in pregnancy (Huisman, 2015). Shown in Figure 52-2 is one diagnostic algorithm recommended by the American College of Chest Physicians that can be used for evaluation of pregnant women (Guyatt, 2012). With a few modifications, we follow a similar evaluation at Parkland Hospital.

DEEP VEIN THROMBOSIS: ALGORITHM FOR EVALUATION



DEEP VEIN THROMBOSIS

- Compression Ultrasonography
- In pregnant women with suspected deep-vein thrombosis, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend compression ultrasonography of the proximal veins as the initial diagnostic test. According to the American College of Chest Physicians, this noninvasive technique is currently the most-used first-line test to detect deep-vein thrombosis (Guyatt, 2012). The diagnosis is based on the noncompressibility and typical echoarchitecture of a thrombosed vein.

- For nonpregnant patients with suspected thrombosis, the safety of withholding anticoagulation for 1 week has been established for those who have a compression ultrasound examination that is initially normal (Birdwell, 1998; Heijboer, 1993). Serial compression examinations are then performed because isolated undetected calf thromboses that ultimately extend into the proximal veins will do so within 1 to 2 weeks of presentation in approximately a fourth of patients.
- In pregnant women, the important caveat is that normal findings with venous ultrasonography do not always exclude a pulmonary embolism. This is because the thrombosis may have already embolized or because it arose from iliac or other deep-pelvic veins, which are less accessible to ultrasound evaluation (Goldhaber, 2004). As discussed, thrombosis associated with pulmonary embolism during pregnancy commonly originates in the iliac veins.
- The results of two studies are helpful for evaluating the need for serial examinations in pregnant women suspected of having a deep-vein thrombosis but who have a negative initial compression ultrasound examination. The combined results are depicted in Figure 52-3. Chan and coworkers (2013) studied 221 pregnant and postpartum women presenting with a suspected deep-vein thrombosis. The 205 women with a negative initial study result underwent serial testing, which was negative in all cases. Of these, one woman with normal serial testing had a pulmonary embolism 7 weeks later. Le Gal and colleagues (2012) studied 210 pregnant and postpartum women with a suspected deep-vein thrombosis. Of these, 177 women without a deep-vein thrombosis were not anticoagulated and did not undergo serial testing. Two had an objectively confirmed thrombosis diagnosed within 3 months. In sum, these preliminary data suggest that a negative single complete compression ultrasonography study may safely exclude the diagnosis of deep-vein thrombosis in most pregnant women.
- ultrasound examinations in pregnant and postpartum women. CUS = compression ultrasonography. DVT = deep vein thrombosis. VTE = venous thromboembolism. (Data from Chan, 2013; Le Gal, 2012.)

- Magnetic Resonance Imaging
- This imaging technique allows excellent delineation of anatomical detail above the inguinal ligament. Thus, in many cases, magnetic resonance (MR) imaging is immensely useful for diagnosis of iliofemoral and pelvic vein thrombosis. The venous system can also be reconstructed using MR venography (Chap. 46, p. 911). Erdman and associates (1990) reported that MR imaging was 100-percent sensitive and 90-percent specific for detection of venographically proven deep-vein thrombosis in nonpregnant patients. Importantly, almost half of those without deep-vein thrombosis were found to have nonthrombotic conditions that included cellulitis, myositis, edema, hematomas, and superficial phlebitis.
- Khalil and coworkers (2012) used MR venography to study the natural history of pelvic vein thrombosis after vaginal delivery. Among the 30 asymptomatic patients who were all within four days of delivery, 30 percent had a definitive thrombosis in either the iliac or ovarian veins, and another 37 percent had a suspected thrombosis. Our experiences with hundreds of postpartum MR scans do not support these findings. Thus, although the clinical significance of their findings is uncertain, it seems clear that some degree of pelvic vein intraluminal filling defect may be a normal finding.

- D-Dimer Screening Tests
- These specific fibrin degradation products are generated when fibrinolysin degrades fibrin, as occurs in thromboembolism (Chap. 41, p. 783). Their measurement is frequently incorporated into diagnostic algorithms for VTE in nonpregnant patients (Wells, 2003). Screening with the D-dimer test in pregnancy, however, is problematic for several reasons. As shown in the Appendix (p. 1256), depending on assay sensitivity, D-dimer serum levels rise with gestational age along with substantively elevated plasma fibrinogen concentrations (Murphy, 2015). Levels are also affected by multifetal gestation and cesarean delivery (Morikawa, 2011). D-Dimer concentrations can also be elevated in certain pregnancy complications such as placental abruption, preeclampsia, and sepsis syndrome. Moreover, higher levels have been observed in sickle-cell carriers and in women of African and South Asian racial origin (Grossman, 2016). For all these reasons, their use during pregnancy remains uncertain, but a negative D-dimer test should be considered reassuring (Lockwood, 2012; Marik, 2008).

- Management
- Optimal management of VTE during pregnancy has not undergone major clinical study to provide evidence-based practices. There is, however, consensus for
- treatment with anticoagulation and limited activity. If thrombophilia testing is performed, it is done before anticoagulation. Heparin induces a decline in antithrombin levels, and warfarin lowers protein C and S concentrations. The results of these tests do not change treatment (Connors, 2017).
- Anticoagulation is initiated with either unfractionated heparin (UFH) or LMWH. Although either type is acceptable, most recommend one of the LMWHs (Bates, 2016; Kearon, 2016). For example, the American College of Chest Physicians suggests preferential use of LMWH during pregnancy because of better bioavailability, longer plasma half-life, more predictable dose response, reduced risks of osteoporosis and thrombocytopenia, and less frequent dosing (Bates, 2012). Dosages are shown in Table 52-5.
- During pregnancy, heparin therapy is continued, and for postpartum women, anticoagulation is begun simultaneously with warfarin. Recall that pulmonary embolism develops in as many as 60 percent of patients with untreated venous thrombosis, and anticoagulation decreases this risk to less than 5 percent. In nonpregnant patients, the mortality rate with a pulmonary embolism approximates 1 percent (Douketis, 1998; Pollack, 2011).
- Over several days, leg pain dissipates. After symptoms have abated, graded ambulation is begun. Elastic stockings are fitted, and anticoagulation is continued.
- Recovery to this stage usually takes 7 to 10 days. Graduated compression stockings are continued for 2 years after the diagnosis to reduce the incidence of postthrombotic syndrome (Brandjes, 1997). This syndrome can include chronic leg paresthesias or pain, intractable edema, skin changes, and leg ulcers.

- Unfractionated Heparin
- This agent should be considered for the initial treatment of thromboembolism and in situations in which delivery, surgery, or thrombolysis may be necessary (American College of Obstetricians and Gynecologists, 2017b). Unfractionated heparin can be administered by one of two alternatives: (1) initial intravenous therapy followed by adjusted-dose subcutaneous UFH given every 12 hours; or (2) twice-daily, adjusted-dose subcutaneous UFH with doses adjusted to prolong the activated partial thromboplastin time (aPTT) into the therapeutic range 6 hours postinjection (Bates, 2012). As shown in Table 52-5, the therapeutic dose for subcutaneous UFH is usually 10,000 units or more every 12 hours.
- For intravenous therapy, several protocols are acceptable. In general, if UFH is used, it is initiated with a bolus intravenous dose of 70 to 100 U/kg, which is 5000 to 10,000 U. This is followed by continuous intravenous infusions beginning at 1000 U/hr or 15 to 20 U/kg/hr. This infusion rate is titrated to achieve an aPTT 1.5 to 2.5 times control values (Brown, 2010; Linnemann, 2016). Intravenous anticoagulation is maintained for at least 5 to 7 days, after which treatment is converted to subcutaneous heparin to maintain the aPTT to at least 1.5 to 2.5 times control throughout the dosing interval. For women with lupus anticoagulant, aPTT does not accurately assess heparin anticoagulation, and thus anti-factor Xa levels are preferred.
- The duration of full anticoagulation varies, and no studies have defined the optimal duration for pregnancy-related thromboembolism. In nonpregnant patients with VTE, evidence supports a minimum treatment duration of 3 months (Kearon, 2012). For pregnant patients, the American College of Chest Physicians recommends anticoagulation throughout pregnancy and postpartum for a minimum total duration of 3 months (Bates, 2012). Lockwood (2012) recommends that full anticoagulation be continued for at least 20 weeks followed by prophylactic doses if the woman is still pregnant. Prophylactic doses of subcutaneous UFH can range from 5000 to 10,000 U every 12 hours titrated to maintain an anti-factor Xa level of 0.1 to 0.2 U/mL, measured 6 hours after the last injection. If the VTE occurs during the postpartum period, Lockwood (2012) recommends a minimum of 6 months of anticoagulation treatment.

- Low-Molecular-Weight Heparin
- This is a family of derivatives of unfractionated heparin, and their molecular weights average 4000 to 5000 daltons compared with 12,000 to 16,000 daltons for
- anticoagulant activity by activating antithrombin. The primary difference is their relative inhibitory activity against factor Xa and thrombin. Specifically, UFH has equivalent activity against factor Xa and thrombin, but LMWHs have greater activity against factor Xa than against thrombin. They also have a more predictable anticoagulant response and fewer bleeding complications than UFH because of their better bioavailability, longer half-life, dose-independent clearance, and decreased interference with platelets (Tapson, 2008). These LMWH compounds are cleared by the kidneys and must be used cautiously when there is renal dysfunction.
- Several studies have shown that VTE is treated effectively with LMWH (Quinlan, 2004; Tapson, 2008). Using serial venograms, Breddin and associates (2001) observed that these compounds were more effective than UFH in reducing thrombus size without increasing mortality rates or major bleeding complications. Several different treatment regimens using adjusted-dose LMWH for treatment of acute VTE are recommended by the American College of Obstetricians and Gynecologists (2017b,c) and are listed in Table 52-5

TABLE 52-5. Anticoagulation Regimen Definitions

Anticoagulation Regimen	Definition
Prophylactic LMWH[a]	Enoxaparin, 40 mg SC once daily Dalteparin, 5,000 units SC once daily Tinzaparin, 4,500 units SC once daily
Therapeutic LMWH[b]	Enoxaparin, 1 mg/kg every 12 hours Dalteparin, 200 units/kg once daily Tinzaparin, 175 units/kg once daily Dalteparin, 100 units/kg every 12 hours May target an anti-Xa level in the therapeutic range of 0.6–1.0 units/mL for twice daily regimen; slightly higher doses may be needed for a once-daily regimen.
Minidose prophylactic UFH	UFH, 5,000 units SC every 12 hours
Prophylactic UFH	UFH, 5,000–10,000 units SC every 12 hours UFH, 5,000–7,500 units SC every 12 hours in first trimester UFH 7,500–10,000 units SC every 12 hours in the second trimester UFH, 10,000 units SC every 12 hours in the third trimester, unless the aPTT is elevated
Therapeutic UFH[b]	UFH, 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5–2.5) 6 hours after injection
Postpartum anticoagulation	Prophylactic LMWH/UFH for 4–6 weeks or vitamin K antagonists for 4–6 weeks with a target INR of 2.0–3.0, with initial UFH or LMWH therapy overlap until the INR is 2.0 or more for 2 days
Surveillance	Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep-vein thrombosis or pulmonary embolism

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SC, subcutaneously; UFH, unfractionated heparin.
[a]Although at extremes of body weight, modification of dose may be required.
[b]Also referred to as weight adjusted, full treatment dose.
Reproduced with permission from American College of Obstetricians and Gynecologists Women's Health Care Physicians: ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy, Obstet Gynecol. 2013 Sep;122(3):706–717.

- harmacokinetics in Pregnancy
- LMWHs available for use in pregnancy include enoxaparin, tinzaparin, and dalteparin. Enoxaparin (Lovenox) pharmacokinetics were studied in 36 women with VTE during pregnancy or immediately postpartum (Rodie, 2002). The dose was approximately 1 mg/kg given twice daily based on early pregnancy weight. Treatment was monitored by peak anti-factor Xa activity at 3 hours postinjection, with a target therapeutic range of 0.4 to 1.0 U/mL. In 33 women, enoxaparin provided satisfactory anticoagulation. In the other three women, dose reduction was necessary. None developed recurrent thromboembolism or bleeding complications. In postcesarean women with a body mass index (BMI) ≥35, Stephenson and associates (2016) found that weight-based dosing of enoxaparin 0.5 mg/kg twice daily more effectively achieved prophylactic peak anti-Xa levels between 0.2 to 0.6 U/mL than a fixed dose of 40 mg daily. Similar findings were reported by Overcash and colleagues (2015).
- For tinzaparin (Innohep), a dosage of 75 to 175 U/kg/d was necessary to achieve peak anti-factor Xa levels of 0.1 to 1.0 U/mL (Smith, 2004). In studies of dalteparin (Fragmin) pharmacokinetics, conventional starting doses of dalteparin— 100 U/kg every 12 hours—were likely insufficient to maintain full anticoagulation (Barbour, 2004; Jacobsen, 2003). Thus, slightly higher doses than that shown in Table 52-5 may be required.
- Dosing and Monitoring
- Standard prophylactic and therapeutic dosages recommended by the American College of Obstetricians and Gynecologists (2017b) for various LMWHs are listed in Table 52-5. Whether such dosages require adjustments during the course o
- pregnancy is controversial (Berresheim, 2014; Cutts, 2013). Some suggest periodic measurement of anti-factor Xa levels 4 to 6 hours after an injection with dose adjustment to maintain a therapeutic level. Large studies using clinical end points that demonstrate an optimal therapeutic range or show that dose adjustments increase therapy safety or efficacy are lacking. Accordingly, the American College of Chest Physicians and others note that routine monitoring with anti-Xa levels is difficult to justify (Bates, 2012; McDonnell, 2017).

- Safety in Pregnancy
- Early reviews concluded that LMWHs were safe and effective (Lepercq, 2001; Sanson, 1999). Despite this, in 2002, the manufacturer of Lovenox warned that its use in pregnancy had been associated with congenital anomalies and a higher risk of hemorrhage. After its own extensive review, the American College of Obstetricians and Gynecologists (2017b) concluded that these risks were rare, that their incidence was not higher than expected, and that no cause-and-effect relationship had been established. It further concluded that enoxaparin and dalteparin could be given safely during pregnancy. Other reports confirm their safety (Andersen, 2010; Bates, 2012; Galambosi, 2012).
- Nelson-Piercy and coworkers (2011) assessed the safety of tinzaparin through a comprehensive study of 1267 treated pregnant women. There were no maternal deaths or complications from regional analgesia. Although thrombocytopenia developed in 1.8 percent, there were no cases of heparin-induced thrombocytopenia (p. 1015). The allergy incidence was 1.3 percent. Osteoporotic fractures in three women (0.2 percent) were judged to be related to tinzaparin (p. 1015). A total of 43 women (3.4 percent) required medical intervention for bleeding. Of 15 stillbirths, four were judged as possibly being related to tinzaparin use. But, none of the neonatal deaths or congenital abnormalities was attributed to tinzaparin. The authors concluded that tinzaparin during pregnancy was safe for mother and fetus. LMWHs are also safe during breastfeeding (Lim, 2010).
- However, LMWHs should be avoided in women with renal failure. Moreover, when given within 2 hours of cesarean delivery, these agents raise the risk of wound hematoma (van Wijk, 2002).

- Labor and Delivery
- Women receiving either therapeutic or prophylactic anticoagulation should be converted from LMWH to the shorter half-life UFH in the last month of pregnancy or sooner if delivery appears imminent. The purpose of conversion to UFH has less to do with any risk of maternal bleeding at the time of delivery, but rather with neuraxial blockade complicated by an epidural or spinal hematoma (Chap. 25, p. 496). The American College of Chest Physicians recommends that women scheduled for a planned delivery who are receiving twice-daily adjusted-dose subcutaneous UFH or LMWH discontinue their heparin 24 hours before labor
- induction or cesarean delivery (Bates, 2012). Patients receiving once-daily LMWH should take only 50 percent of their normal dose on the morning of the day before delivery. The American College of Obstetricians and Gynecologists (2017c) advises that adjusted-dose subcutaneous LMWH or UFH can be discontinued 24 to 36 hours before an induction of labor or scheduled cesarean delivery. The American Society of Regional Anesthesia and Pain Medicine advises withholding neuraxial blockade for 10 to 12 hours after the last prophylactic dose of LMWH or 24 hours after the last therapeutic dose (Horlocker, 2010).
- If a woman begins labor while taking UFH, clearance can be verified by an aPTT. Reversal of heparin with protamine sulfate is rarely required and is not indicated with a prophylactic dose of heparin. For women in whom anticoagulation therapy has temporarily been discontinued, pneumatic compression devices are recommended.

- Anticoagulation with Warfarin Compounds
- Vitamin K antagonists are generally contraindicated because they readily cross the placenta and may cause fetal death and malformations from hemorrhages (Chap. 12, p. 247). They do not accumulate in breast milk and are thus safe during breastfeeding.
- Postpartum venous thrombosis is usually treated with intravenous heparin and oral warfarin initiated simultaneously. The initial dose of warfarin is usually 5 to 10 mg for the first 2 days. Subsequent doses are titrated to achieve an international normalized ratio (INR) of 2 to 3. To avoid paradoxical thrombosis and skin necrosis from the early anti-protein C effect of warfarin, these women are maintained on therapeutic doses of UFH or LMWH for 5 days and until the INR is in a therapeutic range for 2 consecutive days (American College of Obstetricians and Gynecologists, 2017c; Stewart, 2010).
- Treatment in the puerperium may require larger doses of anticoagulant. Brooks and colleagues (2002) compared anticoagulation in postpartum women with that of age-matched nonpregnant controls. The former required a significantly larger median total dose of warfarin—45 versus 24 mg—and a longer time—7 versus 4 days—to achieve the target INR.
- Newer Agents
- Of newer oral anticoagulants, dabigatran (Pradaxal) inhibits thrombin. Rivaroxaban (Xarelto) and apixaban (Eliquis) inhibit factor Xa. Currently, very few reports address these newer agents during pregnancy, and thus the human reproductive risks are essentially unknown (Bates, 2012). Dabigatran crosses the human placenta (Bapat, 2014). However, it is unknown whether any of these agents are excreted in breast milk. Because of the potential for infant harm, a decision should be made to either avoid breastfeeding or use an alternative anticoagulant, such as warfarin, in postpartum women (Burnett, 2016).

- Complications of Anticoagulation
- Three significant complications associated with anticoagulation are hemorrhage, thrombocytopenia, and osteoporosis. The latter two are unique to heparin, and their risk may be reduced with LMWHs. The most serious complication is hemorrhage, which is more likely if there has been recent surgery or lacerations. Troublesome bleeding also is more likely if the heparin dosage is excessive. Unfortunately, management schemes using laboratory testing to identify when a heparin dosage is sufficient to inhibit further thrombosis, yet not cause serious hemorrhage, have been discouraging.
- Heparin-Induced Thrombocytopenia
- There are two types—the most common is a nonimmune, benign, reversible thrombocytopenia that develops within the first few days of therapy and resolves in approximately 5 days without therapy cessation. The second is the severe form of heparin-induced thrombocytopenia (HIT), which results from an immune reaction involving IgG antibodies directed against complexes of platelet factor 4 and heparin. The diagnosis of HIT is based on a drop in the platelet count of more than 50 percent or thrombosis beginning 5 to 10 days after the start of heparin in association with the appearance of platelet-activating HIT antibodies. The fall in platelet count in HIT occurs rapidly—over a period of 1 to 3 days—and is assessed relative to the highest platelet count after the start of heparin. The typical nadir is 40,000 to 80,000 platelets per microliter (Greinacher, 2015).
- Although the incidence of HIT is approximately 3 to 5 percent in nonpregnant individuals, it is <0.1 percent in obstetrical patients (Linkins, 2012). Fausett and coworkers (2001) reported no cases among 244 heparin-treated gravidas compared with 10 among 244 nonpregnant patients. Accordingly, the American College of Chest Physicians recommends against platelet count monitoring when the risk of HIT is considered to be less than 1 percent. In others, they suggest monitoring every 2 or 3 days from day 4 until day 14 (Linkins, 2012).
- When HIT is diagnosed, heparin therapy is stopped and alternative anticoagulation initiated. Platelet transfusions are avoided (Greinacher, 2015). LMWH may not be entirely safe because it has some cross reactivity with UFH. The American College of Chest Physicians recommends danaparoid (Orgaran)—a sulfated glycosaminoglycan heparinoid (Bates, 2012; Linkins, 2012). In a review of nearly 50 pregnant women with either HIT or a skin rash, Lindhoff-Last and associates (2005) concluded that danaparoid was a reasonable alternative. However, they reported two fatal maternal hemorrhages and three fetal deaths. Magnani (2010) reviewed case reports of 83 pregnant women treated with danaparoid. Although it was generally effective, two patients died related to bleeding, three patients suffered nonfatal major bleeds, and three women developed thromboembolic events unresponsive to danaparoid. The drug has been removed from the U.S. market.
- Other agents are fondaparinux (Arixtra)—a pentasaccharide factor Xa inhibitor and argatroban (Novastan)—a direct thrombin inhibitor (Kelton, 2013; Linkins, 2012). Successful use in pregnancy has been reported (Elsaigh, 2015; Knol, 2010). Tanimura and coworkers (2012) successfully used argatroban, and later fondaparinux, to manage HIT in a pregnant woman with hereditary antithrombin deficiency.

- Heparin-Induced Osteoporosis
- Bone loss may develop with long-term heparin administration—usually 6 months or longer—and is more prevalent in cigarette smokers. UFH can cause osteopenia, and this is less likely with LMWHs (Deruelle, 2007). Women treated with any heparin should be encouraged to take an oral daily 1500-mg calcium supplement (Cunningham, 2005; Lockwood, 2012). In one study, Rodger and colleagues (2007) found that long-term use of dalteparin for a mean of 212 days was not associated with a significant decline in bone mineral density.
- Anticoagulation and Abortion
- The treatment of deep-vein thrombosis with heparin does not preclude pregnancy termination by careful curettage. After the products are removed without trauma to the reproductive tract, full-dose heparin can be restarted in several hours.
- Anticoagulation and Delivery
- The effects of heparin on blood loss at delivery depend on several variables: (1) dose, route, and timing of administration; (2) number and depth of incisions and lacerations; (3) intensity of postpartum myometrial contractions; and (4) presence of other coagulation defects. Blood loss should not be greatly increased with vaginal delivery if the episiotomy is modest in depth, there are no lacerations, and the uterus promptly contracts. Unfortunately, such ideal circumstances do not always prevail. For example, Mueller and Lebherz (1969) described 10 women with antepartum thrombophlebitis treated with heparin. Three women who continued to receive heparin during labor and delivery bled remarkably and developed large hematomas. Thus, heparin therapy generally is stopped during labor and delivery. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend restarting UFH or LMWH no sooner than 4 to 6 hours after vaginal delivery or 6 to 12 hours after cesarean delivery. We wait at least 24 hours to restart therapy after cesarean delivery or after vaginal delivery with significant lacerations.
- Slow intravenous administration of protamine sulfate generally reverses the effect of heparin promptly and effectively. It should not be given in excess of the amount needed to neutralize the heparin, because it also has an anticoagulant effect.

- SUPERFICIAL VENOUS THROMBOPHLEBITIS
- Thrombosis limited strictly to the superficial veins of the saphenous system is treated with analgesia, elastic support, heat, and rest. If it does not soon subside or if deep-vein involvement is suspected, appropriate diagnostic measures are performed. Superficial vein thrombosis raises the risk of deep-vein thrombosis four- to sixfold. Heparin is given if deep-vein involvement is confirmed (Roach, 2013). Superficial thrombophlebitis is typically seen in association with varicosities or as a sequela of an indwelling intravenous catheter.

- PULMONARY EMBOLISM
- Although it causes approximately 10 percent of maternal deaths, pulmonary embolism is relatively uncommon during pregnancy and the puerperium. The incidence averages 1 in 7000 pregnancies. According to Marik and Plante (2008), 70 percent of gravidas presenting with a pulmonary embolism have associated clinical evidence of deep-vein thrombosis. And recall that between 30 and 60 percent of women with a deep-vein thrombosis will have a coexisting silent pulmonary embolism.
- Clinical Presentation
- In almost 2500 nonpregnant patients with a proven pulmonary embolism, symptoms included dyspnea in 82 percent, chest pain in 49 percent, cough in 20 percent, syncope in 14 percent, and hemoptysis in 7 percent (Goldhaber, 1999). Pollack and coworkers (2011) found similar symptoms. Other predominant clinical findings typically include tachypnea, apprehension, and tachycardia. In some cases, an accentuated pulmonic closure sound, rales, and/or friction rub is heard.
- Right axis deviation and T-wave inversion in the anterior chest leads may be evident on the electrocardiogram. In at least 40 percent, chest radiography results are normal. In others, nonspecific findings may include atelectasis, an infiltrate, cardiomegaly, or an effusion (Pollack, 2011). Vascular markings in the lung region supplied by the obstructed artery can be lost. Although most women are hypoxemic, a normal arterial blood gas analysis does not exclude pulmonary embolism. Approximately a third of young patients have PO2 values >80 mm Hg.
- Thus, the alveolar-arterial oxygen tension difference is a more useful indicator of disease. More than 86 percent of patients with acute pulmonary embolism will have an alveolar-arterial difference >20 mm Hg (Lockwood, 2012). Even with massive pulmonary embolism, signs, symptoms, and laboratory data to support the diagnosis may be deceptively nonspecific.

MASSIVE PULMONARY EMBOLISM

- This is defined as embolism causing hemodynamic instability (Tapson, 2008). Acute mechanical obstruction of the pulmonary vasculature causes increased vascular resistance and pulmonary hypertension followed by acute right ventricular dilation. In otherwise healthy patients, significant pulmonary hypertension does not develop until 60 to 75 percent of the pulmonary vascular tree is occluded (Guyton, 1954). Moreover, circulatory collapse requires 75- to 80-percent obstruction. This is depicted schematically in Figure 52-4 and emphasizes that most acutely symptomatic emboli are large and likely a saddle embolism. These are suspected when the pulmonary artery pressure is substantively increased as estimated by echocardiography.
- If there is evidence of right ventricular dysfunction, the mortality rate approaches 25 percent. This compares with a 1-percent rate without such dysfunction (Kinane, 2008). It is important in these cases to infuse crystalloids carefully and to support blood pressure with vasopressors. As discussed on page 1018, oxygen treatment, endotracheal intubation, and mechanical ventilation are completed preparatory to thrombolysis, filter placement, or embolectomy (Tapson,

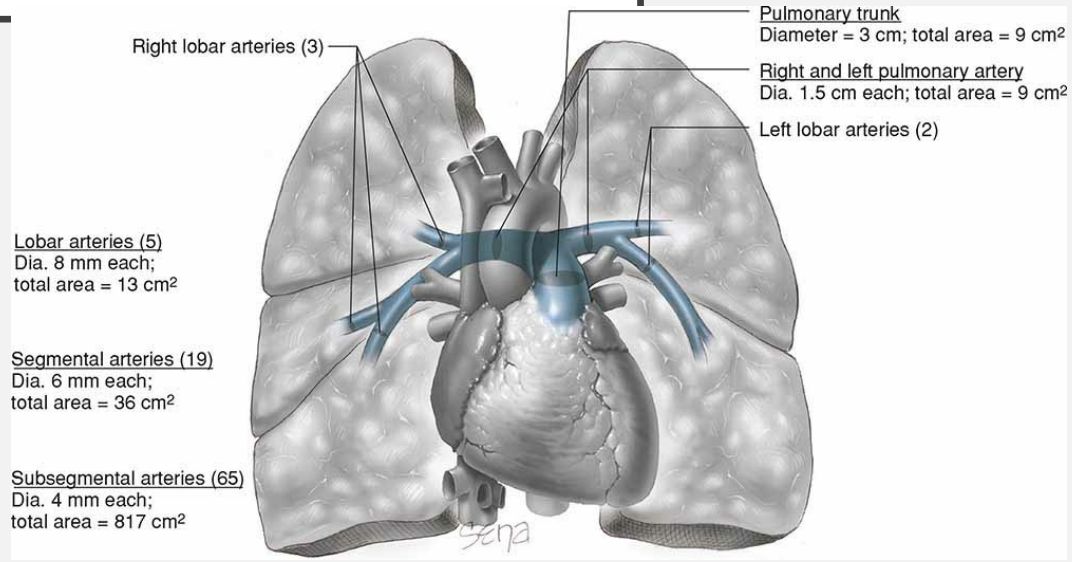


FIGURE 52-4 Schematic of pulmonary arterial circulation. Note that the cross-sectional area of the pulmonary trunk and the combined pulmonary arteries is 9 cm^2. A large saddle embolism could occlude 50 to 90 percent of the pulmonary tree, causing hemodynamic instability. As the arteries give off distal branches, the total surface area rapidly increases, that is, 13 cm^2 for the combined five lobar arteries, 36 cm^2 for the combined 19 segmental arteries, and more than 800 cm^2 for the total 65 subsegmental arterial branches. Thus, hemodynamic instability is less likely with emboli past the lobar arteries. (Data from Singhal S, Henderson R, Horsfield K, et al: Morphometry of the human pulmonary arterial tree, Circ Res. 1973 Aug;33(2):190–197.)

- Diagnosis
- In most cases, recognition of a pulmonary embolism requires a high index of suspicion that prompts objective evaluation. Exposure of the mother and fetus to ionizing radiation is a concern when investigating a suspected pulmonary embolism during pregnancy. However, this concern is largely overruled by the hazards of missing a potentially fatal diagnosis. Moveover, erroneously assigning a diagnosis of pulmonary embolism to a pregnant woman is also fraught with problems. It unnecessarily exposes the mother and fetus to the risks of anticoagulation treatment and will impact delivery plans, future contraception, and thromboprophylaxis during subsequent pregnancies. Therefore, investigations should aim at diagnostic certainty (Konstantinides, 2014).
- In 2011, the American Thoracic Society and the Society of Thoracic Radiology developed an algorithm—shown in Figure 52-5 for the diagnosis of pulmonary embolism during pregnancy (Leung, 2011). In addition to compression ultrasonography, which was previously discussed (p. 1010), the algorithm includes computed-tomographic pulmonary angiography (CTPA) and ventilation-perfusion scintigraphy.

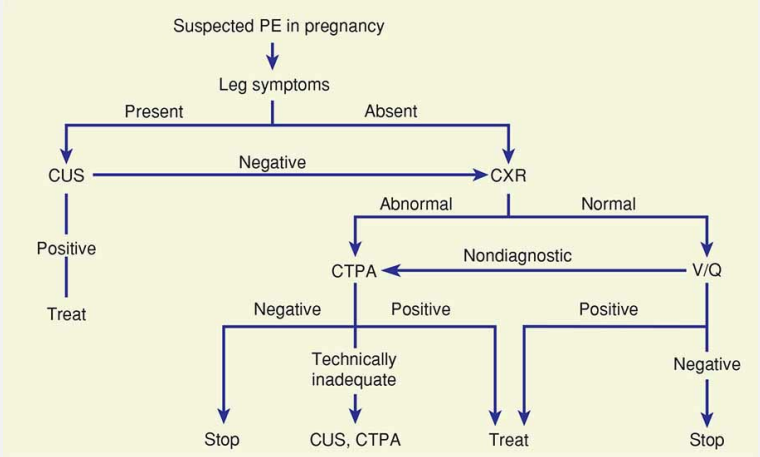


FIGURE 52-5 The American Thoracic Society and Society of Thoracic Radiology diagnostic algorithm for suspected pulmonary embolism during pregnancy. CTPA = computed tomographic pulmonary angiography; CUS = compression ultrasonography; CXR = chest x-ray; PE = pulmonary embolism; V/Q = ventilation/perfusion scintigraphy. (Modified with permission from Leung AN, Bull TM, Jaeschke R, et al: An official American Thoracic Society/Society of

- Computed Tomographic Pulmonary Angiography
- Multidetector computed tomography with pulmonary angiography is currently the most commonly employed technique used for pulmonary embolism diagnosis in nonpregnant patients (Bourjeily, 2012; Pollack, 2011). The technique is described further in Chapter 46 (p. 907), and an imaging example is shown in Figure 52-6. The estimated fetal radiation exposure averages 0.45 to 0.6 mGy. The estimated maternal breast dose is 10 to 70 mGy (Waksmonski, 2014) CTPA has many advantages, but we find that the higher resolution allows
- detection of previously inaccessible smaller distal emboli that have uncertain clinical significance. Similar observations have been reported by others (Anderson, 2007; Hall, 2009). Also, the hyperdynamic circulation and augmented plasma volume associated with pregnancy leads to a higher number of nondiagnostic studies compared with nonpregnant patients (Ridge, 2011; Scarsbrook, 2006).
- Ventilation–Perfusion Scintigraphy—Lung Scan
- This technique involves a small dose of radiotracer such as intravenously administered technetium-99m–macroaggregated albumin. There is negligible fetal and maternal breast radiation exposure—0.1 to 0.4 mGy. The scan may not provide a definite diagnosis because many other conditions can cause perfusion defects. Examples are pneumonia or local bronchospasm. Chan and coworkers (2002) found that a fourth of ventilation-perfusion scans in pregnant women were nondiagnostic. In these instances, CTPA is preferred (Tromeur, 2017).
- To compare the performance of lung scintigraphy and CTPA, Revel and colleagues (2011) evaluated 137 pregnant women with suspected pulmonary embolism. The two modalities performed comparably and had no significant differences between the proportions of positive, negative, or indeterminate results. Specifically, the proportion of indeterminate results for both approximated 20 percent. By way of comparison, about a fourth of the nonpregnant population had indeterminate studies. The investigators attributed this difference to the younger age of the pregnant patients. Similarly, one systematic review concluded that both CTPA and lung scintigraphy seem appropriate for exclusion of pulmonary embolism during pregnancy (van Mens, 2017).

- Intravascular Pulmonary Angiography
- This requires catheterization of the right side of the heart and is considered the reference test for pulmonary embolism. With newer generation multidetector CT scanners, however, the role of invasive pulmonary angiography has been questioned. This is especially true given the higher radiation exposure for the fetus (Konstantinides, 2014; Kuriakose, 2010). Other detractions are that it can be time consuming, uncomfortable, and associated with dye-induced allergy and renal failure. Indeed, the procedure-related mortality rate approximates 1 in 200 (Stein, 1992). It is reserved for confirmation when less invasive tests are equivocal.
- Management
- Immediate treatment for pulmonary embolism is full anticoagulation similar to that for deep-vein thrombosis as discussed on page 1012. Several complementary procedures may be indicated.

- Vena Caval Filters
- The woman who has very recently suffered a pulmonary embolism and who must undergo cesarean delivery presents a particularly serious problem. Reversal of anticoagulation may be followed by another embolus, and surgery while fully anticoagulated frequently results in life-threatening hemorrhage or troublesome hematomas. In these cases, placement of a vena caval filter should be considered before surgery (Marik, 2008). Moreover, in the very infrequent circumstances in which heparin therapy fails to prevent recurrent pulmonary embolism from the pelvis or legs, or when embolism develops from these sites despite heparin treatment, a vena caval filter may also be indicated. Such filters can also be used following massive emboli in patients who are not candidates for thrombolysis (Deshpande, 2002).
- The device is inserted through either the jugular or femoral vein and can be inserted during labor (Jamjute, 2006). Routine filter placement has no added advantage to heparin given alone (Decousus, 1998). Retrievable filters may be used as short-term protection and then removed 1 to 2 weeks later (Liu, 2012). From their systematic review, Harris and associates (2016) found that complication rates in pregnant women with vena caval filters are comparable to those in nonpregnant patients.

- Thrombolysis
- Compared with heparin, thrombolytic agents provide more rapid lysis of pulmonary clots and improvement of pulmonary hypertension (Tapson, 2008). Konstantinides and coworkers (2002) studied 256 nonpregnant patients receiving heparin for an acute submassive pulmonary embolism. They also were randomly assigned to a placebo or the recombinant tissue plasminogen activator alteplase. Those given the placebo had a threefold greater risk of death or treatment escalation compared with those given alteplase. Agnelli and associates (2002) performed a metaanalysis of trials involving 461 nonpregnant patients. They reported that the risk of recurrence or death was significantly lower in patients given thrombolytic agents and heparin compared with those given heparin alone— 10 versus 17 percent. Importantly, however, there were five—2 percent—fatal bleeding episodes in the thrombolysis group and none in the heparin-only group.
- In their review, Leonhardt and colleagues (2006) identified 28 reports of tissue plasminogen activator use during pregnancy. Ten cases were for thromboembolism. Complication rates were similar to those in nonpregnant patients, and the authors concluded that such therapy should not be withheld during pregnancy if indicated. However, Akazawa and Nishida (2017) reviewed 13 cases of systemic thrombolytic therapy administered during the first 48 hours after delivery. Blood transfusion was required in five of the eight cesarean deliveries, including three cases of hysterectomy and two cases of hematoma removal.

- Embolectomy
- Given the efficacy of thrombolysis and filters, surgical embolectomy is uncommonly indicated. Published experience with emergency embolectomy during pregnancy is limited to case reports (Colombier, 2015; Saeed, 2014). From their review, Ahearn and associates (2002) found that although the operative risk to the mother is reasonable, the stillbirth rate is 20 to 40 percent.

- THROMBOPROPHYLAXIS
- Most recommendations regarding thromboprophylaxis during pregnancy stem from consensus guidelines. In one review of guidelines for thromboprophylaxis in pregnancy, the authors concluded that there is a lack of overall agreement about which women should be offered thromboprophylaxis or offered testing for thrombophilias (Okoroh, 2012). Bates and associates (2016) also conducted a review of guidelines for obstetrically associated VTE. They summarized that evidence-based recommendations are based largely on observational studies and extrapolated from data in nonpregnant patients. Similarly, a Cochrane review concluded that evidence is insufficient for firm recommendations regarding thromboprophylaxis during pregnancy (Bain, 2014).
- The confusion that has ensued has provided fertile ground for litigators. Cleary- Goldman and associates (2007) surveyed 151 fellows of the American College of Obstetricians and Gynecologists and reported that intervention without a clear indication is common. Table 52-6 lists several consensus recommendations for thromboprophylaxis. In some cases, more than one option is listed, thus illustrating the confusion that currently reigns.

SOME RECOMMENDATIONS FOR THROMBOPROPHYLAXIS DURING PREGNANCY

Clinical Scenario	Pregnancy		Postpartum	
	ACOG[a]	ACCP[b]	ACOG[a]	ACCP[b]
Prior single VTE				
Risk factor no longer present	Surveillance only	Surveillance only	Postpartum anticoagulation[c] "Surveillance only acknowledged by some experts."	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Pregnancy- or estrogen-related or no known association (idiopathic) ***and*** not receiving long-term therapy	Prophylactic UFH or LMWH ***or*** "Surveillance only acknowledged by some experts"	Prophylactic or intermediate-dose LMWH	Postpartum anticoagulation[c]	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Receiving long-term warfarin	NSS	Adjusted-dose LMWH ***or*** 75% of a therapeutic dose of LMWH	NSS	Resume long-term anticoagulation
Associated with a high-risk thrombophilia[d] ***and*** not receiving long-term anticoagulation or an affected first-degree relative	Prophylactic, intermediate-, or adjusted-dose LMWH or UFH	NSS	Postpartum anticoagulation[c] ***or*** intermediate- or adjusted-dose LMWH or UFH × 6 weeks[c]	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Associated with a low-risk thrombophilia[e] and not receiving treatment	Prophylactic or intermediate-dose LMWH or UFH ***or*** surveillance only	NSS	Postpartum anticoagulation[c] ***or*** intermediate-dose LMWH or UFH	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks

SOME RECOMMENDATIONS FOR THROMBOPROPHYLAXIS DURING PREGNANCY

Two or more prior VTEs with or without thrombophilia				
Not receiving long-term therapy	Prophylactic or therapeutic-dose UFH or LMWH	NSS	Postpartum anticoagulation[c] ***or*** therapeutic-dose LMWH or UFH × 6 weeks	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Receiving long-term anticoagulation	Therapeutic-dose LMWH or UFH	Adjusted-dose LMWH ***or*** 75% of a therapeutic dose of LMWH	Resumption of long-term anticoagulation	Resumption of long-term anticoagulation
No prior VTE				
High-risk thrombophilia[d]	Surveillance only ***or*** prophylactic or intermediate-dose LMWH or UFH	Prophylactic or intermediate-dose LMWH	Postpartum anticoagulation[c]	Intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Positive family history VTE ***and*** homozygous factor V Leiden or prothrombin 20210A mutation	NSS	Prophylactic or intermediate-dose LMWH	NSS	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks

SOME RECOMMENDATIONS FOR THROMBOPROPHYLAXIS DURING PREGNANCY

Negative family history VTE and homozygous factor V Leiden or prothrombin 20210A mutation	Surveillance only ***or*** prophylactic LMWH or UFH	Surveillance only	Postpartum anticoagulation[c]	Prophylactic- or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Positive family history VTE and low-risk thrombophilias[e]	Surveillance only	Surveillance only	Postpartum anticoagulation[c] ***or*** intermediate-dose LMWH or UFH	Prophylactic or intermediate-dose LMWH ***or*** in women <u>not</u> protein C or S deficient, warfarin target INR 2.0–3.0
Low-risk thrombophilia[e]	Surveillance only	Surveillance only if no family history	Surveillance only; postpartum anticoagulation with additional risk factors[f]	Surveillance only if no family history
Antiphospholipid antibodies				
History of VTE	Prophylactic anticoagulation with UFH or LMWH (?plus low-dose aspirin)	NSS	Prophylactic anticoagulation[c]; referral to specialist[g]	NSS
No prior VTE	Surveillance only ***or*** prophylactic LMWH or UFH ***or*** prophylactic LMWH or UFH plus low-dose aspirin if prior recurrent pregnancy loss or stillbirth	Prophylactic- or intermediate-dose UFH ***or*** prophylactic-dose LMWH, both given with 75–100 mg/day aspirin[h]	Prophylactic heparin plus low-dose aspirin × 6 weeks if prior recurrent pregnancy loss or stillbirth[g]	NSS

CESAREAN DELIVERY

- The risk for deep-vein thrombosis and fatal thromboembolism increases following cesarean compared with that after vaginal delivery.
- American College of Obstetricians and Gynecologists (2017b) recommended placement of pneumatic compression devices before cesarean delivery for all women not already receiving thromboprophylaxis.
- For patients undergoing cesarean delivery with additional risk factors for thromboembolism, both pneumatic compression devices and UFH or LMWH may be recommended.