Clinical Updates in Women’s Health Care

Thrombosis, Thrombophilia, and Thromboembolism

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Objectives
This monograph is designed to enable the obstetrician–gynecologist to do the following:

- Understand the coagulation, anticoagulation, and fibrinolytic systems
- Identify risk factors for venous thromboembolism
- Facilitate counseling of patients at risk to minimize the occurrence of venous thromboembolism
- Understand how to diagnose, treat, and prevent recurrence of thromboembolism

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This revised monograph is an up-to-date review of thromboembolic events that are most commonly encountered in pregnancy and the postpartum period. It is written by two authorities in the field and provides practical, evidence-based information. Venous thromboembolism is a significant cause of maternal mortality in the United States and around the world. In a succinct and systematic manner, the authors present the complicated coagulation cascade and the pathophysiology, risk factors, diagnosis, management, and prevention of venous thromboembolism.

An entire section of the monograph is dedicated to the controversies of adverse pregnancy events, factor V Leiden, and prothrombin gene mutation. The information provided in this section should assist the practicing obstetrician–gynecologist in the diagnosis and management of these conditions. The authors also address the relevance of antithrombin deficiency. Although rarely encountered, this condition is associated with significant risks. Recently discovered gene mutations linked to clotting disorders and their significance also are described in practical terms. Specific recommendations of therapeutic agents, new anticoagulants, and management protocols are described in detail. Several case studies are included to illustrate the specific teaching points. The management algorithms presented in the monograph follow the most recent practice guidelines for the management of common and rare thromboembolic conditions and should serve as an excellent resource for the practicing obstetrician–gynecologist.

Raul Artal, MD
Past Editor
ABSTRACT. Obstetrician–gynecologists are uniquely positioned to identify patients at risk of venous thromboembolism, a leading cause of morbidity and mortality in women. Pregnancy, use of exogenous estrogen, and gynecologic surgery represent three of the most provocative stimuli for venous thromboembolism; therefore, obstetrician–gynecologists should be aware of these and other risk factors, so that preventive measures can be implemented. Furthermore, because venous thromboembolism is increasingly common in these three clinical settings, it is important that obstetrician–gynecologists be fully versed in the diagnosis and treatment of venous thromboembolism.

This monograph describes the basic elements of the coagulation system, risk factors, and diagnostic algorithms for venous thromboembolism as well as various therapeutic agents available to treat venous thromboembolism. Strategies for screening patients who require gynecologic surgery, are planning pregnancy, are currently pregnant, or are using estrogen-containing hormone therapy (HT) also are described.

Venous thromboembolism is a leading cause of death in women (1). Its two principal presentations are 1) deep vein thrombosis (DVT), usually in leg veins, and 2) acute pulmonary embolism (PE). Approximately 90% of cases of the acute PE arise from DVT, particularly when proximal leg veins are the sites of the initial thrombus. The overall annual incidence of venous thromboembolism in the United States has been estimated to be 1.45 per 1,000 individuals, with DVT occurring in 4.8 per 10,000 individuals and acute PE in 2.3 per 10,000 individuals (1). The prevalence of both conditions increases markedly with increasing age. Patients with DVT also are at risk of chronic postphlebitic syndrome, characterized by venous ulceration, pain, and edema. Furthermore, based on claims data, the prevalence of venous thromboembolism is estimated to increase from 0.95 million in 2006 to 1.82 million in 2050 in the United States (2). This increase primarily reflects the aging of the population. Given the substantial mortality and morbidity associated with venous thromboembolism in women and the pathologic contributions of pregnancy, use of exogenous estrogen, and gynecologic surgery, it is important that obstetrician–gynecologists take the lead in identifying patients at risk, implementing preventive measures, promptly diagnosing thrombotic events, and ensuring that therapy is expeditiously initiated.
Platelet Plug Formation

After vascular disruption, platelets initially adhere to subendothelial collagen by the formation of von Willebrand factor (vWF) bridges anchored to collagen at one end and to the platelet GPIb–IX–V receptor at the other end (3) (Fig. 1). Platelets also adhere to other subendothelial extracellular matrix proteins (eg, laminin, fibronectin, and vitronectin) by means of specific integrins. Adherent platelets are activated after such receptor binding, causing the synthesis of thromboxane (TXA₂) and phosphorylation of key platelet proteins that together initiate release of α-granules containing vWF, thrombospondin, platelet factor 4, fibrinogen, β-thromboglobulin, and platelet-derived growth factor as well as dense granules containing adenosine diphosphate (ADP) and serotonin. In turn, ADP induces a conformational change in the GPIIb–IIIa receptor on the platelet membrane, causing platelet aggregation by the formation of high-affinity fibrinogen bridges.

Fig. 1. Platelet plug formation after vascular injury. Abbreviations: ADP indicates adenosine diphosphate; PAF, platelet activating factor; TF, tissue factor; TXA₂, thromboxane.
anchored at either end by GPIIb–IIIa receptors on different platelets. Thus, fibrinogen serves as a focal point for aggregating platelets.

The release of $\alpha$-granules promotes exteriorization of procoagulant factors that contribute to thrombin (factor IIa) generation. Thrombin, in turn, binds to type 1 and type 4 protease-activated receptors on platelet membranes and acts as a key stimulus for further platelet activation. Platelets also can be activated by a panoply of other agents, including epinephrine, arachidonic acid, collagen, $\text{TXA}_2$, ADP, and platelet-activating factor (PAF) (Fig. 1). Blood flow itself impedes platelet aggregation, and inappropriate platelet aggregation also is held in check on intact endothelial cells by elaboration of prostacyclin, nitric oxide, and ADP.

**Fibrin Plug Formation**

Even the most efficient platelet adhesion and aggregation cannot produce a completely effective hemostatic plug after substantial vascular disruption. As noted in the section “Platelet Plug Formation,” effective platelet activation and aggregation require exogenous thrombin generation (Fig. 1). Thus, hemostasis is ultimately dependent on initiation of the coagulation cascade. Tissue factor, a 46 kDa cell membrane-bound glycoprotein, is responsible for the initiation of adequate hemostasis (4). Tissue factor is primarily expressed on the cell membranes of perivascular smooth muscle cells, fibroblasts, and tissue parenchymal cells. After vascular disruption and in the presence of ionized calcium, perivascular cell- or platelet-bound tissue factor comes into contact with plasma factor VII on negatively charged (anionic) cell membrane phospholipids (Fig. 1).

Factor VII is unique among clotting factors in that it has low intrinsic clotting activity and it autoactivates after binding to tissue factor and can be activated by factors IIa, IXa, Xa, or XIIa. The complex of tissue factor–factor VIIa can either directly activate factor X or generate factor Xa by activating factor IX. The latter binds with its cofactor, factor VIIIa, to activate factor X. Once activated, factor Xa binds with its cofactor, factor Va, to convert factor II (prothrombin) to factor IIa (thrombin). Each sequential step results in a progressive amplification of downstream effectors; thus, a small number of factor VIIa molecules can generate a large number of factor Xa molecules, which generates an even larger number of thrombin molecules. Vitamin K hydroquinone ($\text{KH}_2$) is required for normal coagulation because it serves as a cofactor in the $\gamma$-carboxylation of N-terminal glutamates on prothrombin, factor VII, factor IX, and factor X to permit their binding to negatively charged phospholipids through the divalent calcium molecule. The cofactors, factor V and factor VIII, are, in turn, activated by either thrombin or factor Xa (Fig. 1).

In addition to the tissue factor–VIIa pathway of thrombin generation, a second pathway results from generation of factor Xla by thrombin-activated factor XIIa, generally on the surface of activated platelets. Factor XII can be activated by the action of kallikrein and its cofactor, high molecular weight kininogen, as well as by plasmin. Although factor Xla provides an alternative pathway for factor IX activation, the lack of significant hemorrhagic sequelae in patients with factor XI deficiency underscores its relatively minor role in the maintenance of hemostasis.
Thrombin cleaves fibrinogen to produce fibrin. A stable hemostatic plug is then formed when fibrin monomers self-polymerize and cross-link by means of thrombin-activated factor XIIIa (Fig. 1). Thus, thrombin plays a central role and is the ultimate arbiter of clotting because it not only activates platelets and generates fibrin but, along with factor Xa, activates the crucial clotting cofactors, factor V and factor VIII, and mediates the aforementioned activation of factors VII, XI, XII, and XIII (Fig. 1). Thrombin-activation of platelets also promotes exteriorization of negatively charged phospholipids to create additional surfaces for clotting factor generation.

The Anticoagulant System
The hemostatic system is designed to prevent hemorrhage after vascular injury without interfering with the fluidity of blood flow in an intact vasculature. This paradoxical mission is accomplished by the interplay of effector and inhibitor molecules (Fig. 2). The first inhibitory molecule, tissue factor pathway inhibitor, forms a complex with tissue factor VIIa and factor Xa. However, as previously noted, this block can be bypassed by the generation of factor XIa. Thus, additional anticoagulant molecules are required to maintain blood fluidity.

Fig. 2. Anticoagulant system. Abbreviations: aPC indicates activated protein C; EPCR, endothelial protein C receptor; FDP, fibrin degradation product; PAI, plasminogen activator inhibitor; PC, protein C; PS, protein S; PZ, protein Z; TAFI, thrombin-activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; tPA, tissue-type plasminogen activator; uPA, urokinase-type plasminogen activator; ZPI, Z-dependent protease inhibitor.
Ironically, thrombin also plays a central role in regulating the anticoagulant system. After thrombin binds to thrombomodulin, a conformational change permits thrombin to activate protein C when bound to damaged endothelium or to the endothelial protein C receptor. Activated protein C then binds to its cofactor, protein S, to inactivate factors Va and VIIIa. Factor Xa also can be directly inhibited by the protein Z-dependent protease inhibitor. When the Z-dependent protease inhibitor binds to its cofactor, protein Z, its inhibitory activity is enhanced 1,000-fold (5). The Z-dependent protease inhibitor molecule also inhibits factor XIa in a process that does not require protein Z.

The most active inhibitor of both factor Xa and thrombin is antithrombin. Antithrombin binds vitronectin and either thrombin or factor Xa. The resultant conformational change facilitates binding to heparin, which augments thrombin inactivation 5,000-fold to 40,000-fold. A similar thrombin inhibitory mechanism is used by heparin cofactor II and α-2 macroglobulin.

**Fibrinolysis and Its Inhibitors**

The process of fibrinolysis also is crucial to the prevention of thrombosis (Fig. 2). Fibrin is broken down to its degradation products by plasmin. Plasmin is created by the proteolysis of plasminogen mediated by tissue plasminogen activator (TPA) embedded in fibrin. Endothelial cells also produce urokinase plasminogen activator. Activation of the latter requires the intrinsic pathway initiators, ie, factors XIa and XIIa. This phenomenon explains why deficiency of these intrinsic pathway factors leads to thrombosis and not hemorrhage.

Inhibitors of fibrinolysis also exist (Fig. 2). Plasmin is directly inhibited by α₂-plasmin inhibitor. This inhibitor, like plasminogen, can be bound to a fibrin clot, where it is positioned to prevent premature fibrinolysis. Both platelets and endothelial cells release type-1 plasminogen activator inhibitor (PAI-1) in response to thrombin binding to its endothelial protease-activated receptors. In pregnancy, the decidua also is a very rich source of PAI-1, whereas the placenta is the chief source of type-2 plasminogen activator inhibitor (PAI-2) (6). Another fibrinolytic inhibitor is the thrombin-activatable fibrinolysis inhibitor, which also is activated by the thrombin–thrombomodulin complex. By cleaving the C-terminal lysine in fibrin, the thrombin-activatable fibrinolysis inhibitor renders it resistant to cleavage by plasmin. In the initial stages of clot formation, platelets and endothelial cells release PAI-1 to stabilize the early fibrin clot, but, after a delay, endothelial cells release TPA and urokinase plasminogen activator to promote fibrinolysis. This sequence prevents premature fibrinolysis with potential hemorrhage.

**Pathophysiology and Risk Factors**

Vascular stasis, hypercoagulability, and vascular trauma (Virchow triad) remain the three prime antecedents to thrombosis. Clinical risk factors for venous thromboembolism are summarized in Box 1. Each of these risk factors increases clotting potential by contributing
to Virchow triad by increasing levels of tissue factor, other clotting factors, and PAI-1; by decreasing protein S levels; or by increasing stasis or promoting vascular injury.

**Pregnancy**

Pregnancy and delivery present unique and profound challenges to a woman’s hemostatic system. During pregnancy, uterine decidual hemorrhage must be avoided during implantation, placentation, and the third stage of labor. Dramatic changes in local decidual and systemic coagulation, anticoagulant systems, and fibrinolytic systems are required to meet this complex challenge. Progesterone augments perivascular decidual cell tissue factor and PAI-1 expression (6). Underscoring the importance of decidual tissue factor to puerperal hemostasis, transgenic mice with low tissue factor expression have a 14% incidence of fatal postpartum hemorrhage despite having a less invasive placenta than humans (7). In addition, obstetric conditions associated with impaired decidualization (eg, ectopic pregnancy, pregnancy within a scar from previous cesarean delivery, placenta previa, and placenta accreta) are all associated with potential lethal hemorrhage in humans.

Pregnancy is associated with a doubling in concentrations of fibrinogen and 20–1,000% increases in factors VII, VIII, IX, X, and XII, all of which peak at term (8). Levels of vWF also increase up to 400% by term. Conversely, levels of prothrombin and factor V Leiden remain unchanged, whereas levels of factors XIII and XI decrease.

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**Box 1. Clinical Risk Factors for Venous Thromboembolism**

- Age older than 50 years
- Trauma
- Surgery
- Obesity
- Heart failure
- Nephropathy
- Malignancy
- Hyperviscosity syndrome
- Inflammatory bowel disease
- Immobilization or prior stroke
- Presence of infectious disease
- Personal or family history of venous thromboembolism
- Thrombophilia
- Use of estrogen-containing contraceptives and hormonal therapy
- Pregnancy
modestly. However, the net effect of these changes is to increase thrombin-generating potential. Because of increased levels of its carrier protein, the complement 4β-binding protein, pregnancy also is associated with a progressive decrease in free protein S antigen levels, which reach their nadir at delivery. Mean free-protein S antigen levels are 38.9% of the normal level in the second trimester and 31.2% of the normal level in the third trimester (9). As a consequence, pregnancy is associated with an increase in resistance to activated protein C. These effects are exacerbated by cesarean delivery and infection, which increase levels of the complement 4β-binding protein and drive further reductions in free protein S concentrations. Levels of PAI-1 increase threefold to fourfold during pregnancy, whereas plasma PAI-2 concentrations, which are negligible before pregnancy, reach more than 160 micrograms per liter at term. Thus, pregnancy is associated with increased clotting potential, decreased anticoagulant activity, and decreased fibrinolysis, facilitating hemostasis but increasing the risk of venous thromboembolism.

This thrombotic risk is exacerbated by pregnancy-associated venous stasis in the lower extremities caused by compression of the inferior vena cava and pelvic veins by the enlarging uterus as well as a hormone-mediated increase in deep vein capacitance secondary to increased circulating levels of estrogen and local production of prostacyclin and nitric oxide. Thus, venous flow velocity in the legs decreases by approximately 50% by 25–29 weeks of gestation and this decreased state lasts until approximately 6 weeks postpartum (10, 11). The occurrence of venous thromboembolism is increased up to 10-fold during pregnancy and the puerperium with an incidence of approximately 1 per 1,500 (12). Furthermore, compression of the left iliac vein by the right iliac artery is thought to contribute to the 70–90% predominance of left-sided DVT during pregnancy (13). Although many of the physiologic changes that contribute to an increased risk of venous thromboembolism resolve by 6 weeks postpartum, one study noted a significant increase in venous thromboembolism risk through 12 weeks after delivery (14). Because the absolute risk of thrombosis is low between 6 weeks postpartum and 12 weeks postpartum, the clinical implications are uncertain. Nonetheless, measures taken to prevent thrombosis should be considered and assessed for efficacy through 12 weeks postpartum.

In a large retrospective cohort study of 268,525 obstetric patients, an incidence of venous thromboembolism of 165 (0.06%) or 1 per 1,627 births was reported (15). Of these cases, 77% were DVT and 23% were acute PE. Of the affected patients, only 14% (23 of 165) had a history of venous thromboembolism. The location of the DVT was predominantly in the left leg (82%) with 75% of the cases occurring during the antepartum period, of which 50% occurred before 15 weeks of gestation and 29% after 20 weeks of gestation. In contrast, acute PE was diagnosed in 60% of patients during the postpartum period. All three maternal deaths caused by acute PE occurred after cesarean delivery. These findings support the long-held notion that the period of the highest risk for lethal acute PE is after cesarean delivery. In one study of patients undergoing cesarean delivery who developed acute PE, 36% were older than 35 years and 55% were obese (16). The risk of venous thromboembolism during antepartum hospital admission was assessed in a cohort of 206,785 English women aged 15–44 years who had one or more pregnancies
from 1997 to 2010 (17). Antepartum hospital admission was associated with an absolute risk of venous thromboembolism of 17.5 per 1,000 person-years, which was increased (95% confidence interval [CI], 7.69–40) compared with time outside hospital. The rate was highest for patients in the third trimester and for those with a hospital stay of 3 or more days.

**Gynecologic Surgery**

The reported rate of venous thromboembolism after gynecologic surgery is approximately 1 per 500 procedures. Long duration of anesthesia (longer than 3 hours), underlying thrombophilias, and surgery for malignant conditions appear to be primary causes of venous thromboembolism in this setting because patients without these risk factors rarely develop postoperative venous thromboembolism (18). In one study, it was observed that 86% of patients with acute PE who had undergone gynecologic surgery were older than 40 years, whereas 36% were obese and 43% had endometrial carcinoma (16).

**Obesity**

Obesity is one of the most common major risk factors for venous thromboembolism. It is associated with insulin resistance and hyperlipidemia, both of which are associated with increased PAI-1 levels. Obesity more than doubles the risk of venous thromboembolism associated with surgery and the use of estrogen-containing contraceptives (8, 19).

**Exogenous Estrogen Therapy**

Use of combined estrogen–progestin contraceptives and postmenopausal HT is associated with a twofold to sixfold increased relative risk (RR) of venous thromboembolism (20). The incidence of venous thromboembolism among oral contraceptive (OC) users has been reported to be 3.94 per 10,000 exposed woman-years, with risks increasing sharply among women older than 39 years and among those with a body mass index equal to or greater than 35 (calculated as weight in kilograms divided by height in meters squared) (19).

Additional contributing factors for venous thromboembolism risk among users of estrogen-containing contraceptives are smoking, asthma, and general ill health (19). A further modestly increased risk of venous thromboembolism has thought to be associated with the use of third-generation OCs versus second-generation OCs because of the progestin component (drospirenone) (odds ratio, 1.7; 95% [CI], 1.4–2) (21). However, this observation has not been confirmed in subsequent, better-designed studies, and drospirenone-containing OCs are considered a reasonable option for some women (22, 23). Progesterone-only contraceptives are not associated with an increased risk of venous thromboembolism and should not be avoided in at-risk women.

In the Women’s Health Initiative clinical trial of estrogen plus progestin versus placebo, postmenopausal HT was found to be associated with a twofold rate of venous thromboembolism (34 versus 16 per 10,000 person-years, respectively) compared with placebo, and annual rates of DVT and acute PE of 0.26% and 0.16%, respectively (24).
Estrogen-only postmenopausal HT was associated with a 33% increased risk of venous thromboembolism compared with placebo (28 versus 21 per 10,000 person-years, respectively) (25). These findings are consistent with a meta-analysis of 12 observational studies and randomized clinical trials that suggested an RR of venous thromboembolism among current postmenopausal HT users of 2.14 (95% CI, 1.64–2.81), peaking during the first year of use (RR, 3.49; 95% CI, 2.33–5.59) (26).

**Antiphospholipid Antibodies**

The combination of venous thromboembolism, obstetric complications, and antiphospholipid antibodies defines the antiphospholipid syndrome (Box 2) (27). Antiphospholipid antibody-related thrombosis can occur in any tissue or organ except in superficial veins. Antiphospholipid antibodies represent a general class of self-recognition immunoglobulins directed against proteins bound to negatively charged surfaces, usually anionic.

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**Box 2. Revised 2006 Sapporo Criteria for the Classification of Antiphospholipid Syndrome**

- The patient must have at least one of the following clinical criteria:
  - **Thrombosis**: defined as definitive imaging or histologic evidence of one or more venous, arterial, or small vessel thrombosis, not including superficial venous thrombosis; or
  - Adverse pregnancy outcome, including otherwise unexplained fetal death at 10 weeks of gestation or later of a morphologically normal fetus, or one or more preterm births before 34 weeks of gestation due to eclampsia (or preeclampsia), or placental insufficiency, or three or more unexplained embryonic pregnancy losses (ie, before 10 weeks of gestation)

- The patient must have at least one of the following laboratory criteria on two or more occasions at least 12 weeks apart and no more than 5 years before clinical manifestations:
  - Presence of immunoglobulin G (IgG) anticardiolipin antibodies, immunoglobulin M (IgM) anticardiolipin antibodies, or both (greater than 40 micrograms of IgG antibody [GPL] or greater than 40 micrograms of IgM antibody [MPL] or greater than 99th percentile for the testing laboratory)
  - Presence of antibodies to β2-glycoprotein of IgG or IgM greater than 99th percentile for the testing laboratory
  - Lupus anticoagulant activity detected according to published guidelines

phospholipids. Box 3 lists specific classes of antiphospholipid antibodies. The three groups of antiphospholipid antibodies that are most commonly associated with clinical problems are 1) lupus anticoagulants, 2) anticardiolipin antibodies, and 3) anti-β2-glycoprotein-I antibodies.

Venous thrombotic events associated with antiphospholipid antibodies include DVT with or without acute PE, whereas the most common arterial events include cerebral vascular accidents and transient ischemic attacks. The lifetime prevalence of arterial or venous thrombosis in affected patients is approximately 30% with an event rate of 1% per year. These antibodies are present in up to 20% of individuals with venous thromboembolism (27, 28). The occurrence of venous thromboembolism in patients with antiphospholipid antibodies may require a hypercoagulable milieu, such as pregnancy, immobilization, estrogen-containing contraceptive use, or postmenopausal HT, as well as a specific thrombotic trigger, such as malignancy, surgery, or infection.

Because recurrence risks of up to 30% have been reported in patients with antiphospholipid antibodies and a prior venous thromboembolism (27, 28), long-term prophylaxis is required with warfarin titrated to maintain an international normalized ratio (INR) of 2–3. There is a 5% risk of venous thromboembolism during pregnancy and the puerperium among patients with antiphospholipid antibodies despite treatment, and the expert consensus suggests that clinical surveillance and heparin prophylaxis are warranted in women with antiphospholipid antibodies but no prior venous thromboembolism for up to 6 weeks postpartum (27). However, according to the authors of a 2014 study, anticoagulation therapy should be continued for 12 weeks postpartum in these women (14).

**Box 3. Classes of Antiphospholipid Antibodies**

- Antiphospholipid antibodies that are best characterized and most commonly used in clinical care
  - Lupus anticoagulant
  - Anticardiolipin antibodies (immunoglobulin G and immunoglobulin M)
  - Anti-β2-glycoprotein-I antibodies (immunoglobulin G and immunoglobulin M)
- Other antiphospholipid antibodies
  - Anticardiolipin antibodies (immunoglobulin A)
  - Anti-β2-glycoprotein-I antibodies (immunoglobulin A)
  - Antiphosphatidlyserine antibodies
  - Antiphosphatidylethanolamine antibodies
  - Antiprothrombin antibodies
  - Antiannexin V antibodies
These antibodies are associated with obstetric complications, including fetal loss, placental abruption, severe preeclampsia, and fetal growth restriction. The risk is most profound with positive lupus anticoagulant status (29). At least 50% of pregnancy losses in patients with antiphospholipid antibodies occur after the 10th week of gestation (27). A meta-analysis of seven studies, examining the effect of antiphospholipid antibodies on in vitro fertilization (IVF) outcomes, suggests that these antibodies do not appear to be associated with very early pregnancy loss (30). In one analyzed study, no significant association between antiphospholipid antibodies and either clinical pregnancy (OR, 0.99; 95% CI, 0.64–1.53) or live birth rates (OR, 1.07; 95% CI, 0.66–1.75) was reported (30). The authors concluded that measurement of antiphospholipid antibodies is not warranted in patients undergoing IVF. Furthermore, antiphospholipid antibodies can be found in approximately 2% of the general obstetric population, and most patients who have either immunoglobulin M or immunoglobulin G anticardiolipin antibodies have relatively uncomplicated pregnancies. This suggests that, as is the case for antiphospholipid antibody-mediated venous thromboembolism, multiple factors contribute to antiphospholipid antibody-mediated adverse obstetric outcomes.

**Inherited Thrombophilias**

As with antiphospholipid antibodies, inherited thrombophilias are linked to venous thromboembolism. Furthermore, as with antiphospholipid antibodies, the occurrence of venous thromboembolism in patients with an inherited thrombophilia is highly dependent on the presence of other predisposing factors, including pregnancy, use of exogenous estrogen, immobilization, obesity, concomitant thrombophilias, and a personal or family history of venous thromboembolism, as well as the presence of triggering factors, such as trauma, surgery, or infection. Thus, inherited thrombophilias are more properly viewed as susceptibility factors rather than as risk factors. The most common inherited thrombophilias, their inheritance, and their prevalence in the general population and among patients with venous thromboembolism as well as their associated risk of venous thromboembolism are listed in Table 1. Similar data are presented for pregnant patients in Table 2.

**Activated Protein C Resistance and Factor V Leiden Mutations**

Present in 3–15% of select European populations and 3% of African Americans and virtually absent in African and Asian populations, factor V Leiden is the most common heritable thrombophilia (31). It arises from a point mutation in the factor V gene, causing the substitution of a glutamine for an arginine at position 506, the site of cleavage by activated protein C, thus conferring activated protein C resistance. This abnormality is inherited in an autosomal dominant manner because the heterozygous state is thrombogenic. Patients with a single mutation have more than a sixfold increased risk of venous thromboembolism in the nonpregnant state, whereas patients homozygous for the mutation have a 50–100-fold increased risk of venous thromboembolism (Table 1). It is associated with 7–50% of all venous thromboembolism events in the general population (31).
Pregnancy further increases the risk of venous thromboembolism in women with this mutation. Factor V Leiden is associated with more than 40% of venous thromboembolism cases in pregnancy (32). However, given the relatively low incidence of venous thromboembolism in pregnancy, approximately 1 in 1,500, and the high incidence of the mutation in the European-derived populations, the estimated risk of venous thromboembolism among pregnant patients who are heterozygous for factor V Leiden without a personal or strong family history (first-degree relative) of venous thromboembolism is only 0.2% (32). The risk may be greater than 10% among those with such a personal or

| Table 1. Inherited Thrombophilias and Their Association With Venous Thromboembolism |
|-----------------------------------|-------------------------------|-----------------|---------------------------------|
| Thrombophilia (Inheritance)       | Prevalence in European Population (Large Cohort Studies) | Prevalence in Patients With Venous Thromboembolism (Range) | Increased Risk or Odds Ratio of Venous Thromboembolism During Lifetime |
| Factor V Leiden (homozygous)*†     | 0.07%‡                       | Less than 1%‡   | 50–100-fold increased risk      |
| Factor V Leiden (heterozygous)*     | 5.3%                         | 6.6%–50%       | OR, 6.6; 95% CI, 3.8–12        |
| Prothrombin G20210A mutation (homozygous)§ | 0.02%‡             | Less than 1%   | Not available                   |
| Prothrombin G20210A mutation (heterozygous)§ | 2.9%                     | 7.5%           | OR, 5.2; 95% CI, 1.4–19.5      |
| Factor V Leiden and prothrombin G20210A mutation (compound heterozygous)|| 0.17%‡ | 2% | OR, 20; 95% CI, 11.1–36.1 |
| Hyperhomocysteinemia (less than 60% activity)† | Less than 5% | Less than 5% | OR, 3.3; 95% CI, 1.1–10* |
| Antithrombin deficiency (less than 60% activity)† †† | 0.2% | 1–8% | OR, 17.5; 95% CI, 9.1–33.8 |
| Protein S deficiency Heerlen S460P mutation or free S antigen (less than 55% activity)‡‡ | 0.2% | 3.1% | OR, 2.4; 95% CI, 0.8–7.9 |
| Protein C (less than 60% activity)† †† | 0.2% | 3–5% | OR, 11.3; 95% CI, 5.7–22.3 |

**Abbreviations:** CI indicates confidence interval; OR, odds ratio.


§Calculated based on a Hardy–Weinberg equilibrium


**Odds ratios are adjusted for renal disease, folate, and vitamin B12 deficiency.


strong family history of venous thromboembolism (32). Pregnant patients homozygous for the factor V Leiden gene mutation have a 1.5% risk of venous thromboembolism in pregnancy in the absence of a personal or family history of venous thromboembolism (32). Presumably with such a history, homozygous patients are at a high risk (greater than 10%) of venous thromboembolism in pregnancy.

Numerous retrospective cohort and case–control studies have indicated an association between factor V Leiden and pregnancy loss. For example, one meta-analysis reported that factor V Leiden is associated with early pregnancy loss (at less than 13 weeks of gestation) with an OR of 2.01 (95% CI, 1.13–3.58) and with late nonrecurrent fetal loss (at greater than 19 weeks of gestation) with an OR of 3.26 (95% CI, 1.82–5.83) (33). Other retrospective studies have not shown an association with early pregnancy loss (34, 35). However, factor V Leiden was not associated with either early or late pregnancy loss in several large prospective cohort studies (36, 37). In contrast, Lindqvist et al prospectively evaluated 2,480 unselected pregnant women for factor V Leiden at an average gestational age of 12 weeks and observed that affected women had no increased risk of

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### Table 2. Inherited Thrombophilias and Their Association With Venous Thromboembolism in Pregnancy

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Prevalence of Venous Thromboembolism in Pregnancy</th>
<th>Relative Risk</th>
<th>Probability of Venous Thromboembolism During Pregnancy and the Puerperium in Patients Without a Personal or Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden (homozygous)*</td>
<td>Less than 1%†</td>
<td>RR, 25.4; 95% CI, 8.8–66</td>
<td>1.5%</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>44%</td>
<td>RR, 6.9; 95% CI, 3.3–15.2</td>
<td>0.26%</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation (homozygous)‡</td>
<td>Less than 1%†</td>
<td>Not available</td>
<td>2.8%</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation (heterozygous)*</td>
<td>17%</td>
<td>RR, 9.5; 95% CI, 2.1–66.7</td>
<td>0.37%</td>
</tr>
<tr>
<td>Factor V Leiden and prothrombin G20210A mutation (compound heterozygous)*</td>
<td>Less than 1%†</td>
<td>RR, 84; 95% CI, 19–369</td>
<td>4.7%</td>
</tr>
<tr>
<td>Antithrombin (less than 60% activity)* †</td>
<td>1–8%</td>
<td>RR, 119</td>
<td>3–7.2%</td>
</tr>
<tr>
<td>Protein S (less than 55% activity)* ‡</td>
<td>12.4%</td>
<td>Not available</td>
<td>Less than 1%–6.6%</td>
</tr>
<tr>
<td>Protein C (less than 50% activity)* ‡</td>
<td>Less than 14%</td>
<td>RR, 13; 95% CI, 1.4–123</td>
<td>0.8%–1.7%</td>
</tr>
</tbody>
</table>

Abbreviations: CI indicates confidence interval; RR, relative risk.

†Calculated based on a Hardy–Weinberg equilibrium
first-trimester fetal loss or venous thromboembolism but did have an increased risk of second-trimester fetal loss (7.3% versus 2.7%, \( P = .01 \)) (38). Thus, the relationship between the thrombophilia and pregnancy loss remains controversial. Importantly, most women with factor V Leiden have normal pregnancy outcomes and, at worst, it should be considered a minor risk factor for stillbirth rather than its cause.

The link between factor V Leiden (and thrombophilias in general) and other adverse pregnancy events, such as placental abruption, severe preeclampsia, and fetal growth restriction, is even more controversial. In a meta-analysis that involved 2,742 hypertensive women and 2,403 controls, it was concluded that factor V Leiden increased the OR of hypertensive disease of pregnancy by 2.25-fold (1.5–3.38) (39). However, the authors noted that no association could be found in studies published after the year 2000 (OR, 0.97; 95% CI, 0.61–1.54), suggesting a publication bias. In another study, an association between factor V Leiden and other thrombophilias and fetal growth restriction was not detected (40). Lykke et al conducted a nested case–cohort study of pregnant women in Denmark, genotyping 2,032 patients and 1,851 random controls (41). After adjusting for parity, age, smoking, body mass index, and socioeconomic status, the authors noted that factor V Leiden was modestly associated with an increased risk of severe preeclampsia (OR, 1.6; 95% CI, 1.1–2.4), fetal growth restriction (OR, 1.4; 95% CI, 1.1–1.8), placental abruption (OR, 1.7; 95% CI, 1.2–2.4), and a composite risk of adverse outcomes (OR, 1.4; 95% CI, 1.1–1.8) (41). However, factor V Leiden was not associated with any adverse pregnancy outcomes in the prospective cohort studies (36, 37). Similarly Lindqvist et al found no association between factor V Leiden and fetal growth restriction or preeclampsia (38). Thus, although there may be a small association between factor V Leiden and fetal loss after 10 weeks of gestation, it is not convincingly linked to other adverse pregnancy outcomes.

**Prothrombin Gene Mutation**

In 1996, a mutation was discovered in the prothrombin gene (G20210A). The gene was found to cause enhanced transcription and elevated prothrombin levels (31). Although only present in 2–5% of the European population, it accounts for up to 8% of venous thromboembolism in nonpregnant patients (42, 43) and 17% of venous thromboembolism in pregnant patients (32). The risk of venous thromboembolism in pregnant heterozygous patients without a personal or family history of venous thromboembolism is only 0.37–0.5%, but with such a history, the risk is likely greater than 10% (32). Homozygous patients without a personal or family history have a 2.8% risk of venous thromboembolism in pregnancy, whereas such a history likely confers a substantially increased risk of venous thromboembolism (32). Pregnant low-risk patients who are compound heterozygotes for factor V Leiden and prothrombin gene mutations have a 4.7% risk of venous thromboembolism (32).

As with factor V Leiden, conflicting data suggest a link between prothrombin gene mutation and fetal loss. In a meta-analysis, an association between the prothrombin gene mutation and recurrent pregnancy loss at less than 13 weeks of gestation (OR, 2.3; 95%
CI, 1.1–4.8), recurrent pregnancy loss at less than 25 weeks of gestation (OR, 2.6; 95% CI, 1–6.3), and nonrecurrent pregnancy loss at greater than 20 weeks of gestation (OR, 2.3; CI, 1.1–4.9) was noted (33). Also, the prothrombin gene was associated with an OR of 3.58 (95% CI, 1.2–10.61; \( P = .02 \)) for a composite of adverse outcomes in a prospective cohort study of 2,000 nulliparous women, primarily caused by a small increase in the number of placental abruptions (37). However, the mutation was not associated with any adverse outcomes in a retrospective study (41), nor was the prothrombin gene mutation linked with adverse pregnancy outcomes in a large prospective U.S. cohort study of more than 4,000 women (44). Other studies also have failed to demonstrate an association between the G20210A mutation and adverse pregnancy outcomes (45).

Hyperhomocysteinemia

Homozygosity for mutations in the methylenetetrahydrofolate reductase (\( MTHFR \)) gene is the most common cause of hyperhomocysteinemia, particularly in individuals who have folate deficiency. Homozygosity for the \( MTHFR \) C677T and \( MTHFR \) A1298C polymorphisms is present in 10–16% and 4–6% of all Europeans, respectively (46). However, these mutations do not appear to convey an increased risk of venous thromboembolism in nonpregnant women (47) or in pregnant women (48). In contrast, untreated hyperhomocysteinemia has been associated with an increased risk of venous thromboembolism (49). Recent data, though, indicate that an increased level of homocysteine is a weak risk factor for thromboembolism (50). Thus, given the fortification of flour with folate in the United States, it is unlikely that hyperhomocysteinemia is an important risk factor for venous thromboembolism.

Similarly, it has been suggested in meta-analyses that fasting hyperhomocysteinemia is more strongly associated with recurrent pregnancy loss (at less than 16 weeks of gestation) than homozygosity for the \( MTHFR \) C677T mutation (OR, 2.7; 95% CI, 1.4–5.2, and OR, 1.4; 95% CI, 1–2, respectively) (51). There also appears to be a link between hyperhomocysteinemia and placental abruption (OR, 3.5; 95% CI, 1.5–8.1) (52). However, the association between homozygosity of \( MTHFR \) mutations in the absence of hyperhomocysteinemia and preeclampsia, intrapartum fetal growth restriction, and placental abruption remains unproved and most retrospective and prospective studies yield no association (45). Currently, there are no data to support screening for the \( MTHFR \) mutation or hyperhomocysteinemia in pregnant women.

Antithrombin Deficiency

Antithrombin deficiency is considered the most thrombogenic of the heritable thrombophilias. More than 250 discrete mutations have been identified in the antithrombin gene producing highly variable phenotypes associated with either reductions in both antigen and activity (type 1 defects) or normal levels of antigen but decreased activity (type 2 defects) (31). Its population prevalence ranges from 0.02% to 1.1% depending on the cutoff chosen for the antithrombin activity assay (Table 1). It accounts for 1–8% of venous thromboembolism episodes in nonpregnant patients (31) and likely a similar
number in pregnant patients. The risk of venous thromboembolism in pregnancy among patients with antithrombin deficiency without a personal or family history is 3–7% and with a personal or family history, is 11–40% (32). These numbers justify anticoagulation therapy during pregnancy and the postpartum period as well as antithrombin infusion therapy during labor and delivery to reduce the risk of venous thromboembolism.

Antithrombin deficiency also is associated with a significantly increased risk of stillbirth at greater than 28 weeks of gestation (OR, 5.2; 95% CI, 1.5–18.1) but a more modest association with fetal loss at 28 weeks or less of gestation and spontaneous abortion (OR, 1.7; 95% CI, 1–2.8) (34). In one study, it was found to be associated with increased risks of fetal growth restriction (OR, 12.93; 95% CI, 2.72–61.45), placental abruption (OR, 60.01; 95% CI, 12.02–300.46), and preterm delivery (OR, 4.72; 95% CI, 1.22–18.26) but not with preeclampsia (35). One descriptive retrospective study identified 18 pregnancies among nine women with antithrombin deficiency between 1991 and 2005; low molecular weight heparin was used in 12 pregnancies (53). The authors observed three episodes of venous thromboembolism (16.7%), two of which occurred in women not treated with anticoagulation. Ten adverse pregnancy outcomes (55.6%) also were observed, including two miscarriages (11.1%) and two stillbirths—both with fetal growth restriction (11.1%); similarly, in these patients no anticoagulant therapy was administered. There were a total of three cases of fetal growth restriction (33.3%), one case of placental abruption (6.7%), and one case of preeclampsia (6.7%). A decreased incidence of pregnancy complications was observed among women treated with antithrombotic agents. However, despite these scattered reports the condition is too rare to allow for precise ascertainment of obstetric risks. Nonetheless, it should be concluded that affected women are at a high lifetime risk of thrombosis and adverse outcomes when pregnant.

**Protein C and Protein S Deficiencies**

Protein C deficiency results from more than 160 distinct mutations that, like antithrombin deficiency, generate a highly variable phenotype associated with either reductions in both antigen level and activity (type 1 defects) or normal levels of antigen but decreased activity (type 2 defects) (31). Activity levels can be ascertained by either a functional (clotting) assay or a chromogenic assay. As with antithrombin deficiency, estimates of prevalence and thrombotic risk reflect the cutoff values used. Most laboratories use functional activity cutoff values of 50–60% that are associated with prevalence estimates of 0.2–0.3% and an RR for venous thromboembolism of 6.5–12.5 (31, 54) (Table 1 and Table 2).

More than 130 mutations have been linked to protein S deficiency (31). Most patients with protein S deficiency can be characterized as having either low total and free protein S antigen levels (type I) or as having only a low free protein S antigen level because of enhanced binding to the complement 4β-binding protein (type IIa). In one study, 82% of patients with the latter abnormality appeared to harbor a distinct Ser 460 to Pro mutation (protein S Heerlen), which also is associated with either the factor V Leiden mutation or a protein C gene mutation in approximately one half of the patients, suggesting a potential cooperative effect on thrombogenicity (55).
A patient can be screened for protein S deficiency with an activity assay, but this is associated with substantial interassay and intraassay variability in part because of frequently changing physiologic levels of complement 4β-binding protein (56). Thus, detection of free protein S antigen levels of less than 55% in nonpregnant women and less than 30% in pregnant patients appears to correlate most closely with genetic defects (9, 56). Using such criteria, the prevalence of true protein S deficiency is low (0.03–0.13%), and its degree of thrombogenicity is modest (OR, 2.4; 95% CI, 0.8–7.9) (19, 36) (Table 1 and Table 2).

Although the literature is limited, protein S deficiency has been linked to recurrent late fetal loss (at greater than 22 weeks) (OR, 14.7; 95% CI, 1–2,181) or nonrecurrent fetal losses at greater than 22 weeks of gestation (OR, 7.4; 95% CI, 1.3–43) (53). In a meta-analysis, a link was suggested between protein S deficiency and stillbirth (OR, 16.2; 95% CI, 5–52.3), fetal growth restriction (OR, 10.2; 95% CI, 1.1–91), and preeclampsia and eclampsia (OR, 12.7; 95% CI, 4–39.7), not placental abruption (52). In contrast, protein C deficiency was associated with preeclampsia (OR, 21.5; 95% CI, 1.1–414.4) but not with stillbirth, and there were insufficient studies to assess the relationship between protein C deficiency and either placental abruption or fetal growth restriction (52). Too few data exist to make definitive conclusions regarding an association between protein C and protein S deficiencies and adverse fetal outcomes.

**Mutations in Fibrinolytic Pathway Genes**

Two polymorphisms in the promoter region of the plasminogen activator inhibitor type-1 (PAI-1) gene, −675 4G/5G and A844G, have been described. In patients homozygous for the 4G/4G allele, the presence of four instead of five consecutive guanine nucleotides in the promoter region produces a site too small to permit the binding of repressors. The −844 polymorphism affects a binding site for the regulatory protein Ets that has been implicated in the regulation of PAI-1 gene transcription. The prevalence of the 4G/4G genotype in the general population is high with a median value in European populations of approximately 27% (57). Furthermore, most studies have not found any independent relationship between the 4G/4G polymorphism and the development of venous thromboembolism in unselected patients; although it may enhance the risk of venous thromboembolism in patients with other thrombophilias (eg, factor V Leiden). Prospective pregnancy outcome data were collected in 1,733 nulliparous women genotyped for this polymorphism with 459 (26.5%) found to be homozygous for the 4G/4G polymorphism, but these women did not have an excess rate of pregnancy complications (58). No definitive relationship has been demonstrated between the PAI-1 A844G polymorphism and venous thromboembolism or adverse pregnancy outcome.

**Protein Z Deficiency**

Of the 16 polymorphisms detected in the coding region of the protein Z-dependent protease inhibitor gene, two nonsense mutations have been identified that are more often present in patients with venous thromboembolism (4.4%) than in controls (0.8%) (OR, 5.7; 95% CI, 1.25–26) (59). Protein Z deficiency (activity less than the fifth percentile)
has been associated with strokes but not with venous thromboembolism (60). Neither abnormality has been consistently linked to fetal loss.

Thus, a great number of potentially thrombophilic polymorphisms are being uncovered at an ever-increasing pace; yet, little information is available on their thrombogenic phenotype or effect on pregnancy outcomes. Although most do not appear to be highly thrombogenic when present in isolation, they may exert an additive or even synergistic effect on the thrombogenicity of other disorders. This might account for the very modest association between a given thrombophilic state (eg, factor V Leiden or protein S deficiency) and the occurrence of venous thromboembolism or adverse pregnancy outcomes in the general population but the higher rates of venous thromboembolism and associated adverse outcomes in certain families.

**Mechanism of Action of Therapeutic Agents**

**Unfractionated Heparin**

Unfractionated heparin enhances antithrombin activity and factor Xa inhibitor activity while inhibiting platelet aggregation. Unfractionated heparin does not cross the placenta or contaminate breast milk. Adverse effects include hemorrhage, osteopenia, and thrombocytopenia. Hemorrhage risk increases when treatment coincides with surgery or liver disease. Osteopenia is reversible and most strongly correlated with doses of heparin greater than 15,000 units per day for more than 6 months. It is reasonable to provide calcium supplementation (at 1,500 mg of calcium per day) to all patients treated with heparin for prolonged periods, although this practice has unproved efficacy.

Heparin-induced thrombocytopenia occurs in 3% of patients (61). Type I heparin-induced thrombocytopenia occurs within days of heparin exposure, is self-limited, and is not associated with a significant risk of hemorrhage or thrombosis. Type II heparin-induced thrombocytopenia is a rare immunoglobulin-mediated syndrome, paradoxically associated with venous and arterial thrombosis, which occurs 5–14 days after initiation of therapy. Monitoring for heparin-induced thrombocytopenia should include measurement of serial platelet counts every 2–3 days until day 14 or until heparin treatment is stopped, whichever occurs first (62). Because it is difficult to discern between type I and type II, a 50% decrease in platelet count from its maximum pretreatment high level should prompt cessation of therapy and avoidance of any form of heparin administration, including intravenous (IV) flushes. The diagnosis of type II heparin-induced thrombocytopenia can be confirmed by serotonin release assays, heparin-induced platelet aggregation assays, flow cytometry, or solid-phase immunoassays. However, none of the assay results are definitive and they do not predict the risk of paradoxical thrombosis.

The goal of IV unfractionated heparin therapy for an acute venous thromboembolism (DVT or acute PE) is to maintain a blood heparin level of 0.2–0.4 units per milliliter by the protamine sulfate titration assay or an antifactor Xa activity between 0.3–0.6 units per milliliter or an activated partial thromboplastin time (aPTT) between 1.5–2.5 times control (63). Intravenous therapy with unfractionated heparin is associated with
inadequate anticoagulant effects in more than one half of patients in the first 24 hours. Treatment for acute PE can be based on weight with a bolus of 80 units per kilogram followed by infusions of 18 units per kilogram per hour, with the dose adjusted to maintain the aPTT at 1.5–2.3 times control. When compared with the standard heparin nomogram (a bolus of 5,000 units and infusion of 1,000 units per hour), this weight-based strategy resulted in a large number of patients exceeding the aPTT target (97% versus 77%; P < .002) and a lower relative risk of recurrent venous thromboembolism of 5 (CI, 1.1–21.9) without major hemorrhagic sequelae (64).

If patients who receive unfractionated heparin start bleeding or require rapid reversal of the anticoagulant effect, protamine sulfate can be administered by slow IV infusion of less than 20 mg/min, with no more than 50 mg given over 10 minutes. The dose of protamine needed to neutralize heparin can be calculated based on the original heparin dose and the interval since administration. Full neutralization of heparin activity requires 1 mg of protamine sulfate per 100 units of residual circulating heparin, with the amount of heparin remaining in the circulation estimated by assuming a half-life of intravenously administered heparin of 30–60 minutes. If the heparin was administered subcutaneously, repeated small infusions of protamine are required with serial measurements of the aPTT. Antithrombin concentrates can be used in patients with antithrombin deficiency in the peripartum period.

Low Molecular Weight Heparin
An alternative to IV unfractionated heparin therapy is the use of therapeutic subcutaneous low molecular weight heparin. The latter is generated by chemical or enzymatic manipulation of unfractionated heparin to reduce its molecular weight to 4,000–6,500 daltons. The smaller size impedes its antithrombin effects but not antifactor Xa effects. Three forms approved by the U.S. Food and Drug Administration (FDA) are available: 1) dalteparin, 2) enoxaparin, and 3) tinzaparin. All offer advantages over unfractionated heparin, including greater bioavailability after subcutaneous injections, longer half-life, and a closer correlation between anti-Xa activity and body weight, reducing or eliminating the need for laboratory monitoring except in patients who are pregnant, who are morbidly obese, or who have renal failure. The latter conditions result in a great variability in heparin binding, metabolism, volume of distribution, and excretion and mandate serial measurements of antifactor Xa levels 4 hours after injection, until the target value of 0.6–1 units per milliliter is achieved.

This therapy is as safe as and potentially more efficacious than that with unfractionated heparin. Extensive experience with the use of low molecular weight heparin in pregnancy confirms its safety and efficacy. However, regional anesthesia is contraindicated within 24 hours of low molecular weight heparin administration. Therefore, unfractionated heparin should be considered at 36–38 weeks of gestation or earlier if preterm delivery is expected, especially if neuraxial anesthesia is desired.

The risk of type II heparin-induced thrombocytopenia appears lower in patients who receive low molecular weight heparin compared with those who receive unfractionated
heparin and lower still for obstetric patients who receive prophylactic low molecular weight heparin therapy. The risk of heparin-induced thrombocytopenia in such women is less than 1% (65). Thus, compared with women who take unfractionated heparin or anticoagulant doses of low molecular weight heparin, it may not be necessary to screen for thrombocytopenia in those who take prophylactic doses of low molecular weight heparin (62). If patients who receive low molecular weight heparin have bleeding or the effects of the therapy need to be rapidly reversed, caution must be exercised with the administration of protamine. Doses of 1 mg of protamine for every 100 anti-Xa units of low molecular weight heparin can completely normalize aPTT values, but antifactor Xa activity can be reversed only partially (80%).

**Fondaparinux**

In 2001, fondaparinux was approved by the FDA for prophylaxis in orthopedic surgery. It is a synthetic heparin pentasaccharide that creates a complex with the antithrombin binding site for heparin to permit the selective inactivation of factor Xa but not thrombin. This agent does not appear to produce heparin-induced thrombocytopenia. Fondaparinux is excreted in the kidney, has a half-life of 15 hours, and is given as a once-daily subcutaneous injection. Once-daily subcutaneous administration of fondaparinux without monitoring appears as safe and effective as enoxaparin use for the treatment of DVT and unfractionated heparin use for the treatment of acute PE.

This agent has been classified as pregnancy class B by the FDA. In one study, it was used in a small number of pregnant patients without sequelae; however, it was found to be present in umbilical cord plasma at concentrations approximately 10% of those in the maternal plasma, suggesting limited transplacental passage (66). The author of the study noted that fondaparinux levels in umbilical cord blood were well below those required for effective anticoagulation but suggested that a potentially hazardous effect cannot be ruled out. Therefore, the use of fondaparinux in pregnant women might best be limited to those who have no obvious therapeutic alternatives, such as patients with heparin-induced thrombocytopenia type II or severe allergic reactions to heparin.

**Coumarin and Warfarin**

Coumarin is a vitamin K antagonists that blocks the generation of vitamin KH₂. Warfarin serves as a cofactor for the posttranslational carboxylation of glutamate residues to γ-carboxyglutamates on the N-terminal regions of prothrombin and factors VII, IX, and X as well as the anticoagulant agents, protein C and protein S. However, the net effect of vitamin K antagonism is anticoagulation because without γ-carboxylation, these clotting factors cannot attach through divalent ionized calcium ions to negatively charged phospholipids present on damaged endothelial cell or activated platelet membranes.

Therapy is begun with initial doses of 5–10 mg for 2 days. Subsequent doses are determined by monitoring the INR, which is the ratio of the patient’s prothrombin time (PT) over the mean population PT adjusted for the effects of the local laboratory’s thromboplastin (ie, the mixture of tissue factor and phospholipid that initiates clotting in the
PT assay). This is done by comparing the local laboratory’s results with those that would be obtained using the World Health Organization’s thromboplastin standard (ie, the International Sensitivity Index: INR = patient PT/population mean PT). The goal is to achieve an INR of 2–3.

The peak effect of warfarin, the most commonly used vitamin K antagonist, occurs 36–72 hours after initiating therapy, and it has a half-life of 36–42 hours. Genetic variations in anticoagulant response are related to a relatively common mutation in the cytochrome P-450 enzyme gene (2C9), and 10 polymorphisms in the gene encoding vitamin K epoxide reductase complex (VKORC1), which account for approximately 25% of phenotypic variation in warfarin dosages and are categorized into a high-, intermediate-, and low-dose haplotypes (67). Genetic testing is available to aid in determining dosage, but generally is not used. Other effectors of dosage variability include variation in laboratory assays, variable patient compliance, and concomitant medications (68). Aspirin and other nonsteroidal antiinflammatory drugs as well as high doses of penicillin and moxalactam increase the risk of warfarin-associated bleeding by inhibiting platelet function. In addition, because of protein C’s relatively shorter half-life compared with most of the vitamin K-dependent clotting factors, warfarin may initially create a relatively prothrombotic state. Indeed, it may take 6 days to achieve full antithrombotic effects. This is particularly true in pregnancy because of increased levels of factor VIII and activated protein C resistance. Therefore, it is important to treat pregnant patients with therapeutic doses of unfractionated heparin or low molecular weight heparin for 5 days or until the INR reaches a therapeutic range between 2 and 3 for 2 successive days. Warfarin has been shown to be effective for both the primary and secondary prevention of venous thromboembolism, stroke, myocardial infarction, and systemic embolism caused by artificial valves and atrial fibrillation (69).

The duration of therapy is dependent on the severity of the thrombotic event and coexisting thrombogenic risk factors (Table 3). In all clinical settings, the risk of recurrent venous thromboembolism must be weighed against the risk of hemorrhage associated with long-term warfarin therapy (69). Although the anticoagulant effects of warfarin can be reversed with vitamin K or fresh frozen plasma, overdosage should be managed

<table>
<thead>
<tr>
<th>Venous Thromboembolism Event and Risk Factors</th>
<th>Duration of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial venous thromboembolism in the setting of reversible or time-limited (transient) risk factors</td>
<td>3–6 months</td>
</tr>
<tr>
<td>Unexplained (idiopathic) initial venous thromboembolism</td>
<td>6–24 months</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism or initial venous thromboembolism in a setting of thrombogenic thrombophilia (eg, antithrombin deficiency, homozygous factor V Leiden, or antiphospholipid antibodies) or a malignancy</td>
<td>Lifetime (12 months at a minimum)</td>
</tr>
</tbody>
</table>
according to signs, symptoms, and the clinical setting. For example, if patients are found to have elevated INRs (greater than 3) but do not have major bleeding, vitamin K can be given orally. However, if bleeding is present, vitamin K should be administered subcutaneously. Normalization of the INR can occur within 6 hours of administration of a 5-mg oral or subcutaneous dose of vitamin K. Although larger doses may work more quickly, they will render the patient resistant to re-anticoagulation with warfarin. When patients who receive long-term warfarin therapy require surgery and have a low risk of recurrent venous thromboembolism, warfarin administration can simply be stopped approximately 4 days before surgery. For patients at high risk of venous thromboembolism, warfarin administration also should be stopped 4 days before surgery; however, therapeutic (full-dose) unfractionated heparin or low molecular weight heparin administration should be initiated as soon as the INR decreases below therapeutic range. In emergent settings, fresh frozen plasma will replenish clotting factors and can be used with subcutaneous vitamin K to reverse the effects of warfarin.

New Anticoagulants

Traditional anticoagulation therapy with heparin and warfarin is limited by the fairly narrow therapeutic windows and significant interpatient dosage variability of these agents. Also, heparin is relatively ineffective at inhibiting thrombin bound to fibrin and factor Xa bound to activated platelets because of its large molecular weight (70). Thus, two new classes of anticoagulants have been developed to address these limitations: 1) direct thrombin inhibitors and 2) factor Xa inhibitors.

Direct Thrombin Inhibitors

Direct thrombin inhibitors offer advantages over heparin. Their anticoagulant effect is more predictable because, unlike heparin, they are not bound to plasma proteins, do not rely on levels of antithrombin, resist neutralization by platelet factor 4, and inhibit fibrin-bound and circulating thrombin. Their primary disadvantage is that their action cannot be immediately reversed, which can create hemorrhagic risks in the perioperative and peripartum periods and will proscribe or delay epidural and spinal anesthesia (71). Also, they prolong the INR, posing problems with warfarin monitoring. Argatroban and bivalirudin are parenteral agents, whereas dabigatran is an orally active direct thrombin inhibitor. Argatroban is a synthetic direct thrombin inhibitor that competitively binds to thrombin’s active site (71). It was approved for prophylaxis and treatment of type II heparin-induced thrombocytopenia. Argatroban has a short half-life (45 minutes) and is cleared by the liver, making it the direct thrombin inhibitor of choice for patients with renal failure. Its activity can be measured by activated aPTT. Caution is advised when converting to warfarin because this agent may act synergistically to prolong the INR. The agent has been categorized by the FDA as pregnancy class B, but experience with its use in pregnancy is limited.
Bivalirudin (hirulog) is a 20-amino acid synthetic polypeptide analog of hirudin (71). It binds to the active site of thrombin. It has a plasma half-life of 25 minutes after IV injection. It was approved by the FDA in 2000 for use in patients with unstable angina who undergo percutaneous transluminal coronary angioplasty (with aspirin). Excretion is by renal and proteolytic pathways. It can be used in patients with type II heparin-induced thrombocytopenia in need of percutaneous coronary angioplasty.

The orally active direct thrombin inhibitor, dabigatran can be used to prevent venous thromboembolism and arterial thromboembolism after surgery, to manage patients with diagnosed venous thromboembolism, or to prevent stroke in patients with atrial fibrillation. It has been classified by the FDA as pregnancy category C. It should be avoided in pregnancy. Common adverse effects include dyspepsia and gastrointestinal bleeding, which may limit its use. Drug clearance is slowed in patients with renal failure and the drug is not recommended in patients with creatinine clearance less than 15 mL/min or in those who receive hemodialysis. A large number of drugs are associated with the P-glycoprotein efflux transporter systems (eg, ketoconazole, cyclosporine, and amiodarone), which can alter dabigatran potency in vivo, and their use must be assessed before administration. Activity can be assessed by aPTT.

**Factor Xa Inhibitors**

Rivaroxaban is administered orally for the prevention and treatment of venous thromboembolism and prevention of stroke in patients with atrial fibrillation. It has been classified by the FDA as pregnancy category C. Although routine monitoring is not necessary, the activity of rivaroxaban can be assessed by aPTT and INR. As with dabigatran, multiple drugs that inhibit the P-glycoprotein efflux transporter can interact with rivaroxaban, and a complete medication history must be obtained before initiating therapy.

Apixaban is another oral factor Xa inhibitor for use in patients to prevent and treat venous thromboembolism. It carries an FDA black box warning when used to prevent stroke in patients with nonvalvular atrial fibrillation because an increased risk of stroke can occur after discontinuation if patients have not received adequate anticoagulation with another agent. It has been classified by the FDA as pregnancy category B with no reported adverse effects in animal reproductive studies; however, there is little experience with the agent in pregnancy and its use should be avoided. It has little effect on aPTT and INR. As with all these new agents, bleeding is a concern, but there is no antidote for apixaban.

Edoxaban is a once-daily oral agent that is excreted by the kidney. Also, its activity is exacerbated by effected agents, inhibiting the P-glycoprotein efflux transporter system.

There are multiple other anti-factor Xa agents in development and a host of other drugs being studied that interfere with tissue factor–factor VIIa activity. The use of these new agents should be consulted with an experienced hematologist with expertise in new anticoagulation agents. Currently, these anticoagulant agents, including dabigatran, rivaroxaban, and apixaban, are not recommended for use in pregnancy (72).
CASE NO. 1. A 68-year-old woman who is obese, diabetic, and hypertensive, presents with new onset uterine bleeding. Results from an office biopsy indicate a well-differentiated endometrial adenocarcinoma, and she is scheduled for surgery. Her medical history also is remarkable for recurrent DVT and type II heparin-induced thrombocytopenia, confirmed by a positive heparin-induced platelet aggregation test result. She currently is taking warfarin, 5 mg per day.

This case points out the need for a thorough understanding of the mechanisms of action and indications of the increasing number of anticoagulation therapies and treatment of patients with anticoagulation therapy during the perioperative period. In this case, the cessation of warfarin use will be required 4 days before surgery with a confirmation of a normal INR preoperatively. If the patient continues to have an increased INR, 5 mg of vitamin K should be administered subcutaneously. She should be given elastic compression stockings to wear throughout the period when she is not receiving anticoagulation therapy and pneumatic compression boots in the immediate perioperative period. Because she has a history of heparin-induced thrombocytopenia, she can receive fondaparinux during the immediate postoperative period until a therapeutic INR has been achieved with warfarin therapy. Alternative agents include the direct thrombin inhibitors. It is important to avoid low molecular weight heparin, because it is contraindicated in women with prior heparin-induced thrombocytopenia caused by unfractionated heparin use (and vice versa) due to a high recurrence risk.

Screening

Screening patients for risks of venous thromboembolism entails recognizing demographic, anthropometric, clinical, and genetic risk factors. Box 1 lists the most commonly associated clinical risk factors. Of particular interest to the obstetrician–gynecologist is the association of venous thromboembolism with gynecologic surgery, exogenous estrogen therapy, pregnancy, and thrombophilias alone or in various combinations.

Preoperative Risk Assessment

A variety of classification schemes have been proposed for perioperative venous thromboembolism risks (73) (Table 4). However, it is unclear whether these complex scoring systems developed for general surgery are pertinent to gynecologic surgery. The latter presents its own unique thrombotic risks, including the use of lower abdominal retractors and packing that may theoretically compress iliac veins.

Hormones

The use of hormones (ie, estrogen-containing contraceptives or postmenopausal HT) presents a unique thrombogenic risk. These risks are exacerbated by surgery. The risk of postoperative venous thromboembolism in women who take OCs is nearly double that of women who do not take OCs (0.96% versus 0.5%) (74). Similarly, postmenopausal HT was found to increase the risk of intraoperative and postoperative venous thromboembolism nearly threefold among 2,763 women with a mean age of 67 years who had coronary heart disease but no prior venous thromboembolism when undergoing surgery (75).
In this study, HT caused an excess of 3.9 thrombotic events per 1,000 woman-years (95% CI, 1.4–6.4). Multivariate analysis suggested the highest risk groups were women who had lower extremity fractures (relative hazard ratio [HR], 18.1; 95% CI, 5.4–60.4), cancer (relative HR, 3.9; 95% CI, 1.6–9.4), and those who were within 90 days of inpatient surgery (relative HR, 4.9; 95% CI, 2.4–9.8) or nonsurgical hospitalization (relative HR, 5.7; 95% CI, 3–10.8). Conversely, risks were reduced by use of aspirin (relative HR, 0.5; 95% CI, 0.2–0.8) or statins (relative HR, 0.5; 95% CI, 0.2–0.9). Ideally, to avoid the thrombogenic effects attendant to exogenous estrogen therapy, OCs or postmenopausal HT should be stopped for 6–8 weeks before elective surgery.

The risk of thrombosis may be less with postmenopausal estrogen therapy that is administered transdermally rather than orally (76). Orally administered estrogen may induce hepatic production of prothrombotic mediators, which does not happen with transdermal administration. Also, a large case–control study among postmenopausal women aged 45–70 years between 1999 and 2005 in France noted an OR for venous thromboembolism of 4.2 (95% CI, 1.5–11.6) for women taking oral estrogen compared with 0.9 (95% CI, 0.4–2.1) for those taking transdermal estrogen (77). In this study, the use of micronized progesterone and pregnane derivatives was not associated with an elevated risk of thrombosis; however, norpregnane derivatives were linked to an increased risk (OR, 3.9; 95% CI, 1.5–10).

### Table 4. Risk Classification for Venous Thromboembolism in Patients Who Undergo Surgery Without Prophylaxis

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Definition</th>
<th>Successful Prevention Strategies</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td>Surgery lasting less than 30 minutes in patients younger than 40 years with no additional risk factors</td>
<td>No specific prophylaxis; early and aggressive mobilization</td>
</tr>
<tr>
<td>Moderate</td>
<td>Surgery lasting less than 30 minutes in patients with additional risk factors; surgery lasting less than 30 minutes in patients aged 40–60 years with no additional risk factors; and major surgery in patients younger than 40 years with no additional risk factors</td>
<td>Low-dose unfractionated heparin (5,000 units every 12 hours), low molecular weight heparin (2,500 units of dalteparin or 40 mg of enoxaparin daily), graduated compression stockings, or intermittent pneumatic compression device</td>
</tr>
<tr>
<td>High</td>
<td>Surgery lasting less than 30 minutes in patients older than 60 years or with additional risk factors; major surgery in patients older than 40 years or with additional risk factors</td>
<td>Low-dose unfractionated heparin (5,000 units every 8 hours), low molecular weight heparin (5,000 units of dalteparin or 40 mg of enoxaparin daily), or intermittent pneumatic compression device</td>
</tr>
<tr>
<td>Highest</td>
<td>Major surgery in patients older than 60 years plus prior venous thromboembolism, cancer, or molecular hypercoagulable state</td>
<td>Low-dose unfractionated heparin (5,000 units every 8 hours), low molecular weight heparin (5,000 units of dalteparin or 40 mg of enoxaparin daily), or intermittent pneumatic compression device and graduated compression stockings plus low-dose unfractionated heparin or low molecular weight heparin; continuing prophylaxis for 2–4 weeks after discharge should be considered</td>
</tr>
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</table>

CASE NO. 2. A 53-year-old woman has been using HT for 6 months. The therapy was initiated in part because of hot flushes and sleep disturbances. Also, she has developed progressive symptoms of urinary stress incontinence, uterine prolapse, and dyspareunia. The pelvic relaxation symptoms have worsened despite pelvic floor exercises, weight loss, behavioral modification, and HT use, and she is scheduled to have a vaginal hysterectomy, anterior and posterior repair, and a urethral suspension procedure. She says she has no personal history of venous thromboembolism, but her sister had a DVT after the second cesarean delivery.

This case underscores the importance of knowing the effect of estrogen-containing HT as well as a family history of venous thromboembolism on perioperative thrombotic risks. This patient’s use of HT increases her risk of perioperative thrombosis by twofold to threefold. However, because she has a first-degree relative with a history of venous thrombosis, the possibility of an inherited thrombophilia exists, which could increase her risk up to 15-fold. Several different management approaches can be considered for this patient. She could be screened for factor V Leiden and the prothrombin G20210A mutation and, if the results are positive, be considered at high risk of thrombosis (Table 4). Alternatively, she could be considered at high risk based on her family history alone. In either case, HT should be stopped for 8 weeks before the surgery. Because she is older than 40 years, she should receive graduated elastic compression stockings, pneumatic compression prophylaxis, or both in the perioperative period until she is ambulating well postoperatively. If she has a positive screening test result for thrombophilia, consideration should be given to perioperative prophylactic low-dose heparin started before the surgery, and she should receive postoperative prophylaxis throughout the hospitalization and be switched to warfarin for up to 28 days based on the thrombophilic defect identified. No HT should be administered after the finding of an inherited thrombophilia. If she has negative test results for thrombophilia, heparin can be administered starting 12 hours postoperatively until discharge.

Thrombophilias

Thrombophilias increase the risk of venous thromboembolism in patients who are receiving exogenous estrogen therapy, are undergoing surgery, or are pregnant. For example, the risk of venous thromboembolism increases 35–99-fold among patients who use estrogen-containing oral contraceptives and 16-fold among carriers of the factor V Leiden and prothrombin G20210A gene mutations (9). The risks attendant to estrogen-containing OCs and thrombophilias are synergistic. For example, among women who do not use OCs, the annual risk of venous thromboembolism is 5.7 per 10,000 for those who are factor V Leiden carriers compared with just 0.8 per 10,000 for those who are not factor V Leiden carriers (RR, 7.9; 95% CI, 3.2–19.4) (78). However, among women who do not have factor V Leiden, the risk of venous thromboembolism in those who use OCs increases to 3 per 10,000 women compared with 0.8 per 10,000 women for those who do not use OCs (RR, 3.8; 95% CI, 2.4–6). For women who use OCs and have factor V Leiden, the risk increases 30-fold to 28.5 per 10,000 women (RR, 34.7; 95% CI, 7.8–154).
In a meta-analysis, a RR of 2.14 (95% CI, 1.64–2.81) is suggested for venous thromboembolism among patients who take HT that peaks during the first year of HT use (RR, 3.49; 95% CI, 2.33–5.59) (25). However, risks of venous thromboembolism in women with factor V Leiden who use HT are increased up to 15-fold (9).

Although it is tempting to conclude that patients should be screened for thrombophilias before initiating exogenous estrogen therapy, given the high prevalence of these mutations, the rarity of venous thromboembolism even among affected patients, and the enormous expense involved in such screening, it is unlikely that such screening would prove cost-effective. It has been estimated that testing for factor V Leiden alone would need to cost less than $9 per patient to justify such screening (21). Although it is also tempting to consider family history as a screening factor to assess which women warrant thrombophilia testing, this tool is likely to be ineffective (79). Another approach would be to avoid estrogen therapy altogether in such patients. Similarly, such therapy should be avoided in patients with a personal history of venous thromboembolism.

Analogous questions arise concerning screening for thrombophilias among patients who require elective or other nonemergent surgery. Patients with thrombophilias who receive thromboprophylaxis for high-risk surgical procedures (eg, orthopedic procedures) do not appear to be at higher risk for venous thromboembolism than such patients without thrombophilias. This suggests screening is not necessary if thromboprophylaxis is to be implemented. Moreover, it is uncertain whether patients at low risk would benefit from thrombophilia screening. In pregnancy, a patient's thrombophilic state affects the recurrence risk of venous thromboembolism. In one prospective study, 125 pregnant women with prior venous thromboembolism were evaluated, 95 of whom were tested for thrombophilias, including the factor V Leiden and prothrombin G20210A mutations, protein C deficiency, protein S deficiency, and antithrombin deficiency; anticardiolipin antibodies; and lupus anticoagulant (80). The authors withheld antepartum heparin but used anticoagulation therapy for 4–6 weeks postpartum. They observed an overall antepartum recurrent venous thromboembolism rate of 2.4% (0.2–6.9%) but found no recurrences in the 44 women who had no evidence of thrombophilia and whose previous episodes of thrombosis were associated with a temporary risk factor (among which the authors included pregnancy). Among the 51 women who had either a thrombophilia or whose previous venous thromboembolism was considered idiopathic, the antepartum recurrence rate was 5.9% (1.2–16.2%), and, among the 25 thrombophilic patients, the recurrence risk for venous thromboembolism was 16% (4:25) (OR, 6.5; 95% CI, 0.8–56.3). Thus, it would appear prudent to test pregnant patients with a history of venous thromboembolism associated with temporary and reversible risk factors (eg, fractures) because the presence of a thrombophilic state would be an indication for antepartum thromboprophylaxis. Similarly, consideration should be given to screening pregnant women with a strong family history (ie, affected first-degree relatives) of venous thromboembolism if they are likely to be exposed to other risk factors during pregnancy, such as prolonged immobilization or cesarean delivery. In these clinical settings, thromboprophylaxis would be appropriate.
Diagnosis and Evaluation

It was reported that in 90% of cases, acute PE follows DVT and that the former is associated with a 12% in-hospital case fatality rate and a 30% 3-year fatality rate (1). These findings underscore the value of early diagnosis and initiation of therapy as well as meticulous follow-up and long-term anticoagulation therapy. However, the clinical signs and symptoms of venous thromboembolism are neither sensitive nor specific. Indeed, three quarters of patients in whom the diagnosis of either DVT or acute PE is considered do not have the disorder (81, 82). Thus, a high index of suspicion must be maintained, particularly in patients with the risk factors outlined in Box 1, despite a low yield of actual diagnoses.

Deep Vein Thrombosis

Clinical Findings and Risk Scoring Systems

The typically cited signs and symptoms of DVT include erythema, warmth, pain, edema, tenderness, and a positive Homans sign. Among patients with these signs and symptoms, the diagnosis of DVT is confirmed in only one quarter to one third when reliable objective tests are performed (83, 84). The differential diagnosis of these signs and symptoms is broad (Box 4). Generally, the presence of suggestive signs and symptoms in high-risk patients is associated with a significantly increased positive predictive value for a given diagnostic study, which directs the diagnostic algorithm (Fig. 3). One straight-
forward risk assessment model in nonpregnant adults (ie, Wells score) has been proposed (Table 5) (83). With this model, patients with signs and symptoms suggestive of DVT in the high prediagnostic test probability category have a prevalence of confirmed DVT of 85%, with 96% involving the higher risk proximal leg vein. Those in the moderate pretest probability category have a prevalence of DVT of 33%, with 72% involving the proximal leg vein. Those in the low pretest probability category have a prevalence of

**Fig. 3.** Workup of suspected deep vein thrombosis (assumes availability of a sensitive test for D-dimers).
DVT of only 5%, with only 62% involving the proximal leg vein. Regardless of a model used, a central element of the evaluation of patients with suggestive signs and symptoms of DVT is determining their level of risk because the choice and interpretation of subsequent diagnostic test results will depend on this risk category.

Risk scoring systems (eg, Wells score) developed for nonpregnant adults have never been validated in young, healthier, pregnant patients with lesser comorbidities. A prediction rule (LEFt) has been introduced for pregnant women; it consists of the following three variables: 1) symptoms in the left leg [L]; 2) calf circumference difference greater than 2 cm [E]; and 3) first-trimester presentation [Ft]. This rule applies to DVT only in the first trimester. The authors who developed the rule evaluated its performance among 194 pregnant women with suspected DVT, 17 of whom ultimately received the diagnosis (81). They noted that DVT was 17 times more likely with isolated left leg symptomology than with right leg symptomatology, 8 times more likely with first-trimester presentation than in any other trimester, and 18 times more likely with calf circumference differences greater than 2 cm than with any other circumference differences. The authors found no confirmed DVT episodes among the 89 women (46%) with none of the LEFt criteria (95% CI, 0–4.2%) but diagnosed DVT in 7 of the 105 women with at least one LEFt criterion (16.2%; 95% CI, 10.5–24.7%). When two or three variables were present, DVT was diagnosed in 58.3% of women (95% CI, 35.8–75.5%). In a second validation study, the rule’s efficacy was assessed in 157 pregnant women with suspected DVT in whom 13 (8.3%) ultimately received the diagnosis (82). Of women with at least one of the LEFt criterion present, DVT was diagnosed in 13 of 111 (11.7%; 95% CI, 8.3–20.9%) versus 0 of 46 with no criterion present (0.0%;95% CI, 0–7.9%). These two studies indicate that absence of LEFt criteria identifies pregnant women at a low risk of DVT.

### Table 5. Deep Vein Thrombosis Clinical Characteristic Score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Score*</th>
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<tbody>
<tr>
<td>Active cancer</td>
<td>+1</td>
</tr>
<tr>
<td>Immobilization (eg, cast, paralysis, or paresis)</td>
<td>+1</td>
</tr>
<tr>
<td>Recent bed rest more than 3 days or major surgery within the past 4 weeks</td>
<td>+1</td>
</tr>
<tr>
<td>Local tenderness along deep vein system</td>
<td>+1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>+1</td>
</tr>
<tr>
<td>Asymmetric calf swelling greater than 3 cm measured 10 cm below tibial tuberosity</td>
<td>+1</td>
</tr>
<tr>
<td>Pitting edema only in symptomatic leg</td>
<td>+1</td>
</tr>
<tr>
<td>Collateral nonvaricose superficial veins</td>
<td>+1</td>
</tr>
<tr>
<td>Prior deep vein thrombosis</td>
<td>+1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as deep vein thrombosis</td>
<td>–2</td>
</tr>
</tbody>
</table>

*In patients with symptoms in both legs, the more symptomatic leg is used. Pretest probability is calculated as the total score: high, 3 or greater; moderate, 1 or 2; low, 0 or less.

**Diagnostic Tests**

The algorithm outlined in Figure 3 can be used to diagnose DVT with maximal sensitivity and negative predictive value. It assumes the availability of a sensitive test for D-dimers. The D-dimer assay has a decreased accuracy for detecting thrombosis in pregnant, puerperal, and postoperative patients as well as those with superficial thrombophlebitis because these patients have high rates of false-positive results.

The details of this test are discussed in the section “D-Dimer Assay.” Currently, its use in pregnant patients cannot yet be endorsed. Figure 4 outlines an alternative diagnostic paradigm for the diagnosis of DVT when the D-dimer test is unavailable or inappropriate or when a patient is pregnant. Other tests include venous ultrasonography, magnetic resonance imaging (MRI), and contrast venography.

![Fig. 4. Alternative diagnostic paradigm for the diagnosis of deep vein thrombosis when D-dimer test is unavailable or inappropriate.](image-url)
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**Venous Ultrasonography.** Venous ultrasonography with or without color Doppler ultrasonography has become the primary diagnostic modality for evaluating patients at risk of DVT. The ultrasound transducer is first placed over the common femoral vein, beginning at the inguinal ligament and then moved to image the greater saphenous vein, the superficial femoral vein, and the popliteal vein to its trifurcation with the deep veins of the calf. Pressure is applied with the probe to determine whether the vein under examination is compressible. The most accurate ultrasound criterion for diagnosing venous thrombosis is noncompressibility of the venous lumen in a transverse plane under gentle probe pressure, using duplex and color Doppler ultrasonography. The sensitivity and specificity of venous ultrasonography generally is reported to be 90–100% for proximal vein thromboses but thought to be lower with calf vein thromboses (84). This is of some concern because whereas distal thromboses are a rare source of acute PE in the absence of extension, the latter occurs in approximately one third of cases. However, a meta-analysis revealed that ultrasonography correctly identified isolated calf DVT with a sensitivity of 92.5% (81.8–97.9%) and a specificity of 98.7% (95.5–99.9%), yielding an overall accuracy of 97.2% (93.9–99%) (85).

**CASE NO. 3.** A 36-year-old nulligravid woman has been using a low-dose estrogen formulation OC for 9 months and notes the development of calf pain and tenderness in her left leg for several days after an intercontinental flight. She does not report trauma or a personal or family history of venous thromboembolism.

The first step in evaluating this patient is to assess her risk category (Table 5). Although the use of hormonal contraception and travel on a long flight increase the index of suspicion, neither warrants a point on the Wells scoring system. Thus, a reasonable approach is to assess the D-dimer status using a sensitive assay. If the result is negative, reassurance can be given. If the result is positive, venous ultrasonography should be performed. If the ultrasound finding is positive, treatment should be initiated. If the finding is negative, repeated venous ultrasonography in 3–7 days should be considered in view of the OC use. If the new finding is negative, reassurance can be given.

**Magnetic Resonance Imaging.** Magnetic resonance imaging appears to be superior to ultrasonography and perhaps the equivalent of contrast venography in diagnosing DVT, although it is potentially more costly than these other techniques. For acute femoropopliteal DVT, the sensitivity and specificity of MRI are approximately 100%. Furthermore, MRI is more sensitive and accurate than ultrasonography for the detection of pelvic and calf DVT. Available data suggest that the range of sensitivity and specificity for MRI in the diagnosis of all DVT is 80–100% and 90–100%, respectively, with median published rates of 100% for both (84).

**Contrast Venography.** Contrast venography is performed by injecting a contrast agent into a superficial vein on the dorsum of the foot. As the contrast material circulates into the deep vein system, the technician obtains X-ray images of the lower leg and thigh up to the level of the external iliac vein (84). Deep vein thrombosis is diagnosed when
intraluminal filling defects are seen on two or more views, or there is an abrupt cutoff of contrast material. It is the most sensitive test for distal (calf) vein DVT. Its chief advantage is its high accuracy for distal vein thrombosis, but disadvantages include expense, invasiveness, pain, radiation exposure, and the risk of contrast media inducing renal compromise or chemical phlebitis. With improved venous ultrasound equipment and superior alternatives (eg, magnetic resonance and computed tomography [CT] venography), the use of contrast venography has greatly diminished.

**D-Dimer Assays.** Laboratory evaluation of D-dimer concentrations has been advocated as a test to rule out DVT. One meta-analysis included studies that compared the accuracy of the D-dimer test with lower extremity venous ultrasonography or contrast venography in symptomatic patients (86). The results were limited by the inclusion of 23 studies using 21 different D-dimer assays and, not surprisingly, demonstrated a wide variation in assay sensitivity, specificity, and negative predictive values, generally less than 90%. The authors concluded that use of a D-dimer assay as a “standalone” screening test for the diagnosis of DVT is not justified. However, more recently developed D-dimer assays appear to have enhanced sensitivity and specificity. The most accurate and reliable tests for D-dimers are two rapid enzyme-linked immunosorbent assays and a rapid whole-blood assay. The sensitivity of the rapid enzyme-linked immunosorbent assay is greater than 95% and that of the rapid whole-blood assay is approximately 85%. Furthermore, combining a sensitive D-dimer assay with a noninvasive imaging test appears to enhance the accuracy of the test (Fig. 3).

The data pool regarding the efficacy of D-dimer testing in pregnancy is increasing. One study evaluated the sensitivity, specificity, and utility of a whole-blood D-dimer agglutination assay for the diagnosis of DVT in pregnant women in a prospective cohort study of 149 consecutive pregnant women with suspected DVT (87). The prevalence of DVT was 8.7% and the sensitivity of the D-dimer assay was 13 out of 13 patients (100%; 95% CI, 77–100%), whereas the specificity was 81 out of 135 patients (60%; 95% CI; 52–68%), with a negative predictive value of 100% (95% CI, 95–100%). The false-positive rate was 0%, 24%, and 51% in the first, second, and third trimesters, respectively. Based on this study, D-dimer assessment might be a useful “rule-out” study in pregnant patients with suspected DVT. However, its high false-positive rate, especially in the second and third trimesters, make D-dimer assessment a poor “rule-in” study. Three prospective studies (n=389) have been published to date, studying a variety of D-dimer assays for the diagnosis for DVT in pregnancy. Each demonstrated 100% sensitivity but low specificity, ranging from 6% to 23% (87–89). There has been one case report of a negative D-dimer test result in the setting of an acute puerperal calf DVT in a postpartum woman (90).

**Recurrent Deep Vein Thrombosis**

The diagnosis of recurrent DVT presents a particular challenge because venous ultrasound findings remain abnormal in up to 75% of patients for 3–6 months after the initial diagnosis (91). In this setting, a single image may be of no value if previous results are not available for comparison. An increase of more than 4 mm in the compressed diameter of
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A previously involved vein is thought to provide strong evidence of recurrent thrombosis. Consideration should be given to assessment of D-dimers and adjunct imaging with MRI or CT venography. The observation of an intraluminal-filling defect on venography is diagnostic for DVT, and a previous examination is not required for comparison.

Acute Pulmonary Embolism

Clinical Findings

Tachypnea (20 or more breaths per minute) and tachycardia (more than 100 beats per minute) are present in 90% of patients with acute PE but are nonspecific indices of risk (92). Similarly, symptoms, such as dyspnea, pleuritic chest pain, presyncope, and syncope, also are present in up to 90% of patients with acute PE; of these presyncope and syncope are more rare and are indicative of massive emboli (92). The nonspecific nature of these signs and symptoms is reflected in the large differential diagnosis they invoke (Box 5).

As was the case for DVT, the use of risk-scoring systems is helpful in defining high-risk populations in whom subsequent diagnostic tests will have a significantly increased positive predictive value. Table 6 outlines one such scoring system in which patients with a low clinical probability have a prevalence of acute PE of 10% or less, those in the intermediate clinical probability group have a prevalence of approximately 30%, and those in the high probability group have a prevalence of 70% or greater (93).

Box 5. Differential Diagnosis of Acute Pulmonary Embolism

- Viral pneumonia
- Bacterial pneumonia
- Postoperative atelectasis
- Pneumothorax
- Chronic obstructive pulmonary disease
- Congestive heart failure
- Lung cancer
- Musculoskeletal chest wall pain
- Esophageal spasm
- Pericarditis
- Pleuritis
- Anxiety
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Electrocardiography. Electrocardiographic changes may be present in 87% of patients with proven acute PE who do not have an underlying cardiopulmonary disease; however, these findings generally are nonspecific (93). Significant changes generally reflect acute PE with hemodynamic sequelae. In the Urokinase Pulmonary Embolism Trial, it was found that 26–32% of participants with massive acute PE had electrocardiographic manifestations of acute cor pulmonale (ie, S₁Q₃T₃ pattern, right bundle branch block, P wave pulmonale, or right axis deviation) (93). These changes are characteristic of right ventricular overload, strain, or both.

Assessment of Arterial Blood Gasses. Assessments of blood oxygen saturation and arterial blood gases and oxygen saturation are of limited value in diagnosing acute PE because 30% of patients younger than 40 years will have PaₐO₂ greater than 80 mm Hg. In contrast, the alveolar–arterial oxygen tension difference appears to be a more useful indicator of disease with alveolar–arterial differences of more than 20 mm Hg present in 86% of patients with acute PE (94).

Chest X-Ray. Chest X-ray findings may be abnormal in up to 84% of affected patients (94). Common findings include pleural effusion, pulmonary infiltrates, atelectasis, and elevated hemidiaphragm. However, these findings are nondiagnostic because they do not rule out acute PE. Traditional findings of pulmonary infarction, such as Hampton hump or decreased vascularity (Westermark sign) are rare. Conversely, whereas a normal chest X-ray result in the setting of dyspnea, tachypnea, and hypoxemia in a patient without known preexistent pulmonary or cardiovascular disease is suggestive of acute PE, chest X-ray cannot be used to confirm the diagnosis.

### Table 6. Acute Pulmonary Embolism Clinical Characteristic Risk Score*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of deep vein thrombosis</td>
<td>+3</td>
</tr>
<tr>
<td>Alternative diagnosis deemed less likely than pulmonary embolism</td>
<td>+3</td>
</tr>
<tr>
<td>Heart rate greater than 100 beats per minute</td>
<td>+1.5</td>
</tr>
<tr>
<td>Immobilization or surgery in previous 4 weeks</td>
<td>+1.5</td>
</tr>
<tr>
<td>Prior venous thromboembolism</td>
<td>+1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>+1</td>
</tr>
<tr>
<td>Active cancer</td>
<td>+1</td>
</tr>
</tbody>
</table>

*Physicians should exercise great caution when applying this risk categorization scheme to pregnant patients because it has not been validated in this population. Given the thrombogenic nature of pregnancy and the puerperal state, particularly after cesarean delivery, it may be prudent to consider all such patients as high risk.

Clinical probability of acute pulmonary embolism is stratified into the following categories based on the cumulative risk score:

- Low: cumulative score, less than 2
- Intermediate: cumulative score, 2–6
- High: cumulative risk, greater than 6

**Echocardiography.** Large emboli in the main pulmonary artery and its primary branches can result in acute right ventricular failure, the ultimate cause of death in patients with acute PE. More than 80% of patients with acute PE have abnormalities of right ventricular size or function detected by ultrasonography or Doppler ultrasonography (84). Findings include a dilated and hypokinetic right ventricle, tricuspid regurgitation, and absence of preexisting pulmonary arterial or left heart pathology. However, these findings also can be seen with exacerbation of underlying chronic obstructive pulmonary disease. Transesophageal echocardiography with or without contrast appears to improve the imaging of main or right pulmonary artery emboli and, occasionally, of left pulmonary artery clots (84).

**Specific Diagnostic Studies**

**Ventilation–Perfusion Scanning.** Long considered a mainstay of the diagnostic evaluation of suspected cases of acute PE, ventilation–perfusion (V/Q) scanning is performed by imaging both the pulmonary vascular bed and airspace (84). Perfusion scanning is accomplished by injecting isotopically labeled (eg, with 99 mTc) human albumin macroaggregates into the bloodstream where they are deposited in the pulmonary capillary bed. Their topographic distribution is then assessed by a photo scanner. Ventilation scanning entails the inhalation of radiolabeled aerosols (eg, 133 Xe) whose distribution in alveolar spaces is assessed by a gamma camera. The combination of perfusion and ventilation scanning allows the discernment of characteristic patterns that can be used to assign diagnostic probabilities. Large mismatched defects (ie, those associated with abnormal perfusion scanning results but normal ventilation scanning results) are associated with acute PE in 80–96% of patients at high and moderate risk but in only 50% of patients at low risk (84).

The Prospective Investigation of Pulmonary Embolism Diagnosis was a multicenter, collaborative effort designed to determine the sensitivity and specificity of V/Q scanning in patients with signs and symptoms of suspected acute PE (95) (Table 7). Overall, patients with high-probability V/Q scanning results had acute PE in 87.2% of cases, but only 41% of patients with acute PE had high-probability scans (sensitivity of 41% and specificity of 97%). Patients with intermediate-probability scanning results had acute PE in 33.3% of cases, whereas acute PE was present in 13.5% of patients with low-probability scanning results and 3.9% of patients with near-normal or normal scanning results.

Information provided in Table 7 indicates that an acute PE can be present in a substantial percentage of patients with nondiagnostic (low and intermediate probability) V/Q scanning results if there is a high clinical suspicion of acute PE. Conversely, 44% of patients at low risk with a high-probability V/Q scanning result ultimately will not be found to harbor an acute PE. These findings underscore the central requirement of determining the patient’s clinical characteristic risk score (Table 6). These results also delineate the limitations of V/Q scanning as a diagnostic modality. A subanalysis of the Prospective Investigation of Pulmonary Embolism Diagnosis data suggests that when ventilation scanning cannot be performed, isolated perfusion scanning has nearly
identical sensitivity and specificity (84). Levels of radiation to the fetus are low with both \( \text{V/Q} \) scanning and CT pulmonary angiography (0.5–1 mGy) and comparable with background radiation (96–98).

**Computed Tomography Pulmonary Angiography.** This technique requires the continuous movement of a patient through a CT scanner as a contrast bolus is administered (84). In nonpregnant patients, CT pulmonary angiography has become firmly established as the first-line test for the diagnosis of acute PE (99). Two meta-analyses, involving 4,657 and 3,089 patients with suspected acute PE, demonstrated that a negative CT pulmonary angiographic result was associated with a 3-month rate of subsequent venous thromboembolism of 1.4% (95% CI, 1.1–1.8%) and 1.2% (95% CI, 0.8–1.8), respectively. A 3-month rate of fatal acute PE was 0.51% (95% CI, 0.33–0.76%) and 0.6% (95% CI, 0.40–1.1%), respectively (100, 101). These data are superior to those associated with negative IV contrast pulmonary angiographic results. Newer technology, thinner sections, and greater institutional experience appear to improve the accuracy of CT pulmonary angiography for diagnosing subsegmental infarcts and may reduce false-negative results to 5% (84).

In pregnancy, increased cardiac output and blood volume alter the dynamics of contrast medium administration and can result in decreased pulmonary arterial opacification and an increased rate of inadequate studies. Indeed, technically inadequate CT pulmonary angiographic results have been reported to occur in 17–36% of pregnant patients (102–105). Furthermore, CT pulmonary angiography presents a significantly increased amount of radiation to the pregnant woman’s breast than does a \( \text{V/Q} \) scan; 10–60 mGy versus 0.98–1.07 mGy, respectively (106–109).

**Magnetic Resonance Angiography.** As an alternative to CT pulmonary angiography, the use of magnetic resonance angiography was described during the pulmonary arterial phase of the cardiac cycle after an IV bolus of gadolinium (110). Using multiple reviewers,
the authors found an overall sensitivity of 100% and specificity of 95% (87–100%), with positive and negative predictive values of 87% (74–100%) and 100%, respectively. The authors of one study used a real-time, steady-state free precession technique in 62 nonpregnant patients with suspected acute PE and reported a sensitivity of 85% and a specificity of 98% (111).

**Evaluation of Lower Extremities for Venous Thrombosis.** Most cases of acute PE arise from lower extremity DVT. In the general population with suspected acute PE where the actual prevalence is 20–36% and the prevalence of concomitant DVT ranges from 9% to 12%, the number of compression venous ultrasound sessions needed to diagnose one DVT and to avoid further workup is 11 (112, 113). Thus, in stable high-risk patients in whom the results of V/Q scanning or other noninvasive testing are not diagnostic, or even negative, evaluation of leg veins for DVT can establish the need for anticoagulation therapy if a DVT is diagnosed (Fig. 5)

**D-Dimer Assays.** A negative D-dimer concentration (less than 500 ng/mL) measured by a sensitive enzyme-linked immunosorbent assay is associated with a 95% negative predictive value but with only a 25% specificity for the diagnosis of acute PE (84). A meta-analysis of studies, examining the accuracy of D-dimer determinations in the diagnosis of acute PE, showed that the D-dimer enzyme-linked immunosorbent assay format produced a sensitivity of 95% (88–100%) and a specificity of 45% (38–53%) (114). The quantitative rapid enzyme-linked immunosorbent assay format was associated with a sensitivity of 98% (88–100%) and a specificity of 40% (29–50%). In contrast, the

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**Fig. 5.** Diagnostic algorithm to rule out acute pulmonary embolism in a high-risk nonpregnant patient. Abbreviations: CT indicates computed tomography; V/Q, ventilation–perfusion.
whole blood D-dimer assay kit yielded a sensitivity of 82% (74–91%) but a specificity of 63% (54–71%). The authors concluded that a negative result on a quantitative rapid enzyme-linked immunosorbent assay is as diagnostically useful as a normal lung scanning result for excluding acute PE. As was the case of the diagnosis of DVT, the specificity is likely to be significantly decreased in pregnant, puerperal, and postoperative patients as well as in those with superficial thrombophlebitis.

As mentioned previously, in pregnancy, D-dimer testing is neither sensitive nor specific for the diagnosis of an acute PE. One retrospective study of pregnant women at high risk of acute PE found D-dimer assays to have a sensitivity and specificity of 73% and 15%, respectively (115). Thus, not only was there a high false-positive rate, but 27% of cases were missed. Also, multiple case reports exist of false-negative D-dimer assay results in pregnant women with confirmed acute PE (116, 117). The decreased diagnostic efficacy of D-dimer assays for acute PE or DVT in pregnancy may reflect the increased volume of distribution, small clot size, or decreased incidence of coexistent lesions in pregnancy. In any case, D-dimer assays should not be used as an adjunct to the workup of suspected acute PE in pregnancy.

**Diagnostic Algorithms**

In nonpregnant women, the first step in assessment is to determine a level of risk (Table 6). No consensus exists as to whether V/Q scanning or CT pulmonary angiography should be the first-line diagnostic modality, and the choice of approach will depend on the experience of the local imaging team and availability of the technology. Concerns over breast irradiation have led some teams to obtain an initial chest X-ray result and, if the result is normal, proceed to V/Q scanning because in this setting V/Q scanning accuracy is maximal. Furthermore, if a hemodynamically stable patient presents with concomitant signs and symptoms of a DVT, the leg should be imaged first because such a diagnosis will mandate treatment, irrespective of pulmonary findings.

Figure 5 outlines a testing paradigm for nonpregnant patients at high risk. In the 10–30% of symptomatic patients who present with a high clinical probability of acute PE (70–90%), initial evaluations include either CT pulmonary angiography or V/Q scanning. A positive CT pulmonary angiography result or high-probability V/Q scanning result is associated with acute PE in 95% of cases and mandates therapy (Fig. 5). In contrast, a normal or near-normal V/Q scanning result rules out the diagnosis. A negative CT pulmonary angiography result or low- or intermediate-probability V/Q scanning result should be followed by venous ultrasonography of the lower extremities and, if those results are positive, treatment should follow; if the results are negative, magnetic resonance angiography should be considered because of the 40–60% probability of an acute PE despite these negative or equivocal test results (Table 7).

Figure 6 and Figure 7 present testing paradigms for the 25–65% of patients with suspected acute PE with the low clinical probability of PE (5–10%). Briefly, a D-dimer assay is performed and, if the result is negative, the diagnosis is excluded. If a D-dimer assay is
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not available or not appropriate or the result of D-dimer assay is positive, the algorithm outlined in Figure 7 is appropriate. In this scenario, CT pulmonary angiography or V/Q scanning is performed. A positive CT pulmonary angiographic result mandates therapy, whereas a normal or near-normal (negative) V/Q scanning result permits exclusion of the diagnosis because the risk of an acute PE in this setting is only 2% (Table 7). If the V/Q scanning result indicates a low or intermediate probability, these patients have a 4–16% risk of acute PE (118, 119), whereas a negative CT pulmonary angiography scanning result may not be accurate; a small subsegmental acute PE can be missed. Thus, such patients should undergo compression venous ultrasonography of their lower extremities. If the result of venous ultrasonography is negative, the diagnosis is excluded. If the result of venous ultrasonography is positive, treatment is initiated. Conversely, if the V/Q scan indicates a high probability of a PE in a patient at low risk, compression venous ultrasonography again is ordered because many patients at low risk with a high-probability V/Q scan result will be found not to harbor an acute PE. If the result of venous ultrasonography is positive, treatment is initiated. However, if the result is negative, magnetic resonance angiography should be performed because many of these patients do harbor an acute PE. A negative angiographic result effectively rules out the diagnosis, whereas a positive result mandates treatment.

Figure 8 presents the workup of the 25–65% of patients with suspected acute PE who are assigned into the low (5–10%) clinical probability group when D-dimer testing is available and appropriate. ☞
intermediate, or high risk, the likelihood of an acute PE ranges from 16% to 88%. Thus, in these patients, compression venous ultrasonography should be performed and, if the results are positive, a treatment started; if the results are negative, magnetic resonance angiography is performed. If the result of the latter is negative, the diagnosis is excluded; if the result is positive, a treatment is initiated.

The level I evidence-based paradigms outlined in Figure 5 through Figure 8 take advantage of well-validated diagnostic modalities, patient risk categories and, potentially, D-dimer assessment to maximize diagnostic sensitivity and also to avoid the risk
Fig. 8. Workup of the 25–65% of patients with suspected acute pulmonary embolism who are assigned into the intermediate (25–45%) clinical risk category. Abbreviation: V/Q indicates ventilation–perfusion.
of unnecessary anticoagulant therapy, which has major long-term health and financial implications. Physicians also may use ancillary modalities, such as electrocardiography, echocardiography, and arterial blood gas measurement as clinical circumstances dictate.

A simplified strategy for the diagnosis of acute PE has been tested in a large prospective observational study, involving more than 3,000 patients with signs and symptoms suggestive of acute PE (120). In this paradigm, patients were categorized either into an “acute PE unlikely” category (66%) if their Wells score was equal to or less than 4 (Table 6) or into an “acute PE likely” category if their Wells score was greater than 4 (33%). Those classified with the acute PE unlikely-status had D-dimer testing, and acute PE was ruled out if the D-dimer test result was normal. All other patients (ie, with the acute PE-likely status and acute PE-unlikely status with positive D-dimer test results) underwent CT pulmonary angiography, most with the more sensitive multi-detector-row methodology. An acute PE was considered present or excluded based on the CT results. The combination of acute PE-unlikely status and a normal D-dimer test result occurred in 32% of patients who thus avoided additional testing and in whom subsequent nonfatal venous thromboembolisms occurred in only 0.5% (95% CI, 0.2–1.1%) within 3 months. Conversely, CT pulmonary angiography detected acute PE in 20.4% of participants, and these individuals were promptly given anticoagulation therapy. Of the remaining 45.5% of participants in whom the CT pulmonary angiography results were negative, 95% were not treated, and their prevalence of subsequent venous thromboembolism was 1.3% (95% CI, 0.7–2%). Of those with subsequent venous thromboembolism, less than 1% had a fatal acute PE. These data are comparable with the rate of fatal acute PE after a negative contrast pulmonary angiography. Thus, this diagnostic paradigm, using a simple clinical decision tree, D-dimer testing, and state-of-the-art CT angiography may prove to be the optimal screening approach.

**Pulmonary Embolism in Pregnant Patients**

Evidence-based guidelines have been developed by a panel of experts appointed by the American Thoracic Society, the Society of Thoracic Radiology, and the American College of Obstetricians and Gynecologists (121). The panel concluded that in pregnant women with suspected acute PE, D-dimer testing should not be used. Furthermore, given its low yield, compression venous ultrasonography was recommended as the first diagnostic procedure only when the patient had concomitant signs and symptoms of DVT. In contrast, chest X-ray was recommended as the first radiation-associated procedure. If the result of the latter was negative, it was recommended to proceed to V/Q; if the chest X-ray result was positive, it was recommended to proceed to CT pulmonary angiography. Given the risk of mortality when acute PE remains undiagnosed, further diagnostic testing with CT pulmonary angiography rather than clinical management alone is indicated in pregnant women with a nondiagnostic V/Q scan result. In unstable pregnant patients in whom the diagnosis of an acute PE is strongly suspected, anticoagulation should be initiated before diagnostic studies. Alternate diagnostic strategies, such as a transesophageal echocardiogram, should be considered in an intensive care setting. Figure 9 outlines this strategy.
The goal of the treatment of patients with venous thromboembolism is to prevent future thromboembolic events. In the event of acute life-threatening conditions, immediate aggressive treatment sometimes is necessary. This section will outline the specific treatment protocols.

Nonpregnant Women

**Unfractionated Heparin**

Unfractionated heparin is indicated for the acute treatment of hemodynamically unstable patients with acute PE or in those at high risk of bleeding or when thrombolysis is being considered. As noted, the dosage of IV unfractionated heparin for patients with venous thromboembolism can be weight or dosage based, with subsequent dosage modifications predicated on the results of frequent monitoring of the aPTT values. Table 8 and Table 9 present two separate treatment protocols.

Fig. 9. Diagnostic workup of a pregnant patient with suspected acute pulmonary embolism.

The goal is to obtain and maintain an aPTT value of 1.5–2.5 times control values. Plasma heparin can be measured by either a protamine sulfate or antifactor Xa chromogenic assay. Target plasma heparin concentrations of 0.2–0.4 units per milliliter are equivalent to antifactor Xa concentrations of 0.4–0.7 units per milliliter. The aPTT value should not be used to guide unfractionated heparin therapy in patients with lupus anticoagulant. The importance of maintaining a therapeutic heparin level is highlighted by the observation that patients with subtherapeutic aPTT values in the first 24 hours have a
15-fold increase in recurrent venous thromboembolism. Monitoring for heparin-induced thrombocytopenia should include serial platelet count every 2–3 days until day 14 or until the time that heparin is stopped, whichever occurs first. Warfarin therapy is started within 24 hours of commencing heparin therapy. The initial doses of warfarin should be 5–10 mg, daily, for 2 days. Subsequent doses are determined by monitoring the INR. To avoid paradoxical thrombosis and skin necrosis from the early antiprotein C effect of warfarin use, it is important to maintain therapeutic doses of unfractionated heparin for 5 days and until the INR is therapeutic (2–3) for 2 consecutive days. The duration of heparin therapy should be extended for up to 10 days in patients with large iliofemoral thromboses or massive acute PE.

### Table 8. Weight-Based Nomogram for Intravenous Unfractionated Heparin Administration*

<table>
<thead>
<tr>
<th>Activated Partial Thromboplastin Time Value</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 35 seconds (less than 1.2 times the control value)</td>
<td>Repeat 80 units per kilogram bolus, then increase infusion rate by 4 units per kilogram per hour</td>
</tr>
<tr>
<td>35–45 seconds (1.2–1.5 times the control value)</td>
<td>Repeat 40 units per kilogram bolus, then increase infusion rate by 2 units per kilogram per hour</td>
</tr>
<tr>
<td>46–70 seconds (1.6–2.3 times the control value)</td>
<td>No change</td>
</tr>
<tr>
<td>71–90 seconds (2.4–3 times the control value)</td>
<td>Decrease infusion by 2 units per kilogram per hour</td>
</tr>
<tr>
<td>More than 90 seconds (greater than 3 times the control value)</td>
<td>Stop infusion one time per 1 hour, then decrease to 3 units per kilogram per hour</td>
</tr>
</tbody>
</table>

*Initial dose is 80 units per kilogram of body weight, followed by a maintenance dose of 18 units per kilogram per hour with activated partial thromboplastin time values obtained every 6 hours with adjustments made based on the values obtained.

### Table 9. Dosage-Based Protocol for Intravenous Unfractionated Heparin Administration*

<table>
<thead>
<tr>
<th>Activated Partial Thromboplastin Time Value</th>
<th>Bolus</th>
<th>Infusion Stop Time</th>
<th>Rate Change</th>
<th>Repeat Activated Partial Thromboplastin Time Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 50 seconds (less than 1.2 times the control value)</td>
<td>Repeat 5,000-unit bolus</td>
<td>0 minutes</td>
<td>+120 units per hour</td>
<td>In 6 hours</td>
</tr>
<tr>
<td>50–59 seconds (1.2–1.5 times the control value)</td>
<td>0</td>
<td>0 minutes</td>
<td>+120 units per hour</td>
<td>In 6 hours</td>
</tr>
<tr>
<td>60–85 seconds (1.6–2.3 times the control value)</td>
<td>0</td>
<td>0 minutes</td>
<td>0</td>
<td>The following morning</td>
</tr>
<tr>
<td>86–95 seconds (2.4–3 times the control value)</td>
<td>0</td>
<td>0 minutes</td>
<td>−80 units per hour</td>
<td>The following morning</td>
</tr>
<tr>
<td>96–120 seconds (2.4–3 times the control value)</td>
<td>0</td>
<td>30 minutes</td>
<td>−80 units per hour</td>
<td>In 6 hours</td>
</tr>
<tr>
<td>Greater than 120 seconds (greater than 3 times the control value)</td>
<td>0</td>
<td>60 minutes</td>
<td>−160 units per hour</td>
<td>In 6 hours</td>
</tr>
</tbody>
</table>

*Initial dose is 5,000 units, followed by a maintenance infusion of 1,280 units per hour, with activated partial thromboplastin time values obtained every 6 hours and adjustments made as noted. From New England Journal of Medicine, Ginsberg JS, Management of venous thromboembolism, Vol. 335, pages 1816–28. Copyright © 1996 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
**Low Molecular Weight Heparin**

Low molecular weight heparin is the preferred initial therapy in hemodynamically stable patients who are not at high risk of hemorrhage. Meta-analyses suggest that low molecular weight heparin offers several advantages over unfractionated heparin. In one meta-analysis, 22 studies were evaluated and fewer thrombotic complications were observed among patients treated with low molecular weight heparin compared with patients treated with unfractionated heparin (3.6% versus 5.4% [OR, 0.68; 95% CI, 0.55–0.84; 18 trials]), a greater reduction in thrombus size (53% versus 45% [OR, 0.69; 95% CI, 0.59–0.81; 12 trials]), fewer major hemorrhages (1.2% versus 2% [OR, 0.57; 95% CI, 0.39–0.83; 19 trials]), and fewer deaths (4.5% versus 6% [OR, 0.76; 95% CI, 0.62–0.92; 18 trials]) (122). The dosage of low molecular weight heparin will depend on the agent used. For example, the dosage of enoxaparin is 1 mg/kg every 12 hours. The level of antifactor Xa activity is highly correlated with the patient’s body weight; thus, laboratory monitoring is not needed unless patients are pregnant, morbidly obese, or have renal failure because, as noted, these conditions affect low molecular weight heparin binding, bioavailability, and volumes of distribution and excretion. Under these circumstances, monitoring antifactor Xa activities is recommended for all patients in whom therapeutic low molecular weight heparin administration was initiated until therapeutic levels are obtained. Treatment is to be continued for 5–10 days, depending on the severity of the venous thromboembolism. Warfarin is to be started on day 2, and both agents are to be continued for 5 days and until the INR is therapeutic (2–3) for 2 consecutive days.

**CASE NO. 4.** A 68-year-old woman develops dyspnea and tachycardia 48 hours after a vaginal hysterectomy and posterior repair. The patient is obese. A CT pulmonary angiographic result is consistent with PE. She is given low molecular weight heparin but develops acute thrombocytopenia on day 4 of the treatment.

In nonpregnant women, the mainstays of treatment for venous thromboembolism are IV unfractionated heparin or subcutaneous low molecular weight heparin followed by oral anticoagulation therapy. Heparin-induced thrombocytopenia can be the result of benign platelet clumping, which requires no cessation of therapy, or is caused by immunoglobulin-mediated aggregation, which is associated with thrombosis. Although results from specific immunoassays and functional assays can produce a definitive diagnosis, all therapy with heparin should be stopped while awaiting such test results. In this case, the patient has likely already begun taking warfarin, and fondaparinux can be given if needed until the INR is therapeutic. If the patient were more remote from surgery, the use of a direct thrombin inhibitor should be considered.

**Pregnant Women**

Women with new-onset venous thromboembolism during a current pregnancy should receive anticoagulation therapy for at least 20 weeks during the pregnancy, followed by prophylactic therapy. Thus, if the event occurs early in pregnancy, most patients can be switched to prophylactic doses after 20 weeks of treatment. Postpartum patients
require a minimum of 6–12 weeks of anticoagulation therapy. During pregnancy, low molecular weight heparin is the anticoagulant of choice because of its efficacy and safety profile. Neither unfractionated nor low molecular weight heparin crosses the placenta and, thus, poses no teratogenic risk. Postpartum, oral anticoagulation therapy with warfarin may be started and is considered safe in breastfeeding. The primary risks of long-term unfractionated heparin therapy in pregnancy are hemorrhage and osteopenia. Hemorrhage occurrence is increased with concomitant aspirin use and surgery. Osteoporosis is increasingly common with doses of heparin greater than 15,000 units per day, used for more than 6 months. Postpartum bone densitometry may be appropriate in such patients, and it is reasonable for all patients treated with unfractionated heparin to receive 1,500 mg of calcium supplementation per day. Bone mineral density typically recovers after stopping the heparin treatment.

**Unfractionated Heparin**

The goal of therapy for an acute venous thromboembolism in pregnancy is to maintain an antithrombin (aPTT) value between 1.5 times and 2.5 times control when using unfractionated heparin. The dose required may vary greatly among women secondary to interpatient differences in heparin-binding proteins in pregnancy. The aPTT value should be evaluated every 4–6 hours during the initial phase of therapy, and adjustments should be made in the dosage as needed (Table 8 and Table 9). Intravenous unfractionated heparin therapy should be continued for at least 5–10 days or until clinical improvement is noted. Thereafter, therapeutic doses of unfractionated heparin then may be administered subcutaneously every 8–12 hours in order to maintain the aPTT value at 1.5–2 times control, 6 hours after the injection. These regimens should be continued for at least 20 weeks, followed by prophylactic dosages. Prophylactic dosages of unfractionated heparin can range from 5,000 units to 10,000 units, subcutaneously, every 12 hours titrated to maintain an antifactor Xa level of 0.1–0.2 units, 6 hours after the last injection. Patients with highly thrombogenic thrombophilias, such as antiphospholipid syndrome and antithrombin deficiency, those homozygous for the factor V Leiden or prothrombin G20210A gene mutations, or those who are heterozygous for both of these mutations require therapeutic anticoagulation throughout pregnancy.

If vaginal or cesarean delivery occurs more than 4 hours after a patient receives a prophylactic dose of unfractionated heparin, the patient is not at substantial risk for hemorrhagic complications. Protamine sulfate may be administered to those patients with an elevated aPTT value who are receiving prophylactic or therapeutic unfractionated heparin and are about to give birth vaginally or by cesarean delivery.

**Low Molecular Weight Heparin**

Use of low molecular weight heparin has been shown to be effective and safe during pregnancy. For therapeutic purposes, the antifactor Xa level should be maintained at 0.6–1 units per milliliter, 4–6 hours after injection (eg, starting with enoxaparin 1 mg/kg, subcutaneously, every 12 hours). The treatment should continue for 20 weeks and then
prophylactic dosages are given (eg, enoxaparin 40 mg, subcutaneously, every 12 hours, adjusted to maintain antifactor Xa levels at 0.1–0.2 units per milliliter, 4 hours after an injection). It is unclear whether basing dosage on weight is sufficient in pregnant women, whether doses need to be slightly increased due to increased clotting factors on pregnancy, or whether levels should be assessed or adjusted to maintain antifactor Xa levels 0.6–1 unit per milliliter and 0.1–0.2 units per milliliter for 4 hours after injection for therapeutic and prophylactic anticoagulation, respectively. As previously noted, patients with highly thrombogenic thrombophilias require therapeutic anticoagulation administration throughout pregnancy. Because regional anesthesia is contraindicated within 24 hours of administration of therapeutic doses of low molecular weight heparin, unfractionated heparin should be used at 36–38 weeks of gestation or earlier if preterm delivery is expected and the patient desires neuraxial anesthesia.

If vaginal or cesarean delivery occurs more than 12 hours from prophylactic administration or 24 hours from therapeutic administration of doses of low molecular weight heparin, the patient should not experience anticoagulation-related problems with delivery. Protamine may partially reverse the anticoagulant effects of low molecular weight heparin.

Postpartum Considerations

Either unfractionated heparin or low molecular weight heparin can be reinitiated 6 hours after vaginal delivery or 12 hours after cesarean delivery. Warfarin should be started on the first postdelivery day. It is important to maintain therapeutic doses of unfractionated heparin or low molecular weight heparin for 5 days and until the INR reaches the therapeutic range between 2 and 3 for 2 successive days. If the venous thromboembolism occurs in the postpartum period, the patient should receive a minimum of 6 months of anticoagulation treatment (Table 3). In patients who require only thromboprophylaxis, unfractionated heparin or low molecular weight heparin can be used in doses for non-pregnant women (eg, 5,000 units twice daily or 40 mg of enoxaparin daily, respectively).

CASE NO. 5. A 38-year-old woman, gravida 1, para 1, develops acute dyspnea and chest pain 3 days after giving birth by cesarean delivery for failure to progress in labor after a 3-hour second stage complicated by acute chorioamnionitis. The pregnancy had been complicated by gestational diabetes mellitus, which is well controlled by diet. A chest X-ray result is normal and V/Q scan indicates high probability of acute PE.

This patient is at high risk of thrombosis. Pregnancy, surgery, and infections all decrease free protein S levels, virtually assuring a relative acquired protein S deficiency in this setting. Furthermore, pregnancy and diabetes mellitus increase PAI-1 levels, impeding fibrinolysis. To reduce breast irradiation, a chest X-ray should be obtained after initiating therapy, followed by a V/Q scan.
Thrombolytic Therapy

If acute PE is expeditiously diagnosed and treated with either unfractionated heparin or low molecular weight heparin, the mortality rate of patients with acute PE should be less than 10% (123, 124). In contrast, a mortality rate of more than 50% (123, 124) has been reported for patients who were hemodynamically unstable at the time of presentation. This observation has been the impetus for trials of thrombolytic therapy in patients with massive acute PE. However, a meta-analysis of nine randomized, controlled trials that compared thrombolytic agents with IV heparin in patients with acute PE indicates that thrombolytic therapy had no statistically significant effect on mortality (RR, 0.63; 95% CI, 0.32–1.23) or the recurrence of acute PE (RR, 0.59; 95% CI, 0.3–1.18) but was associated with a significantly increased risk of major hemorrhage (RR, 1.76; 95% CI, 1.04–2.98) (125). Furthermore, results were largely unaffected by the clinical severity of the acute PE or the extent of vascular obstruction determined by imaging studies. Thus, it does not appear that thrombolytic therapy confers clear benefit in most patients with acute PE, but it is associated with an increased risk of major hemorrhage. Also, there is no proven benefit to such therapy in patients with massive DVT and no evidence that it prevents postphlebitic syndrome.

Pregnancy poses special concerns for use of thrombolytic therapy, given the risk of abruption and puerperal hemorrhage. Outcomes among 172 pregnant patients treated with thrombolytic therapy were reviewed, and it was reported that the maternal mortality rate was 1.2%, the fetal loss rate was 6%, and the rate of maternal complications from hemorrhage was 8% (126). However, given the limited evidence of benefit of such therapy, its use in pregnant patients should be restricted to those rare life-threatening settings in which the potential benefits of the therapy clearly outweigh the serious attendant risks.

Special Concerns for Older Women

Assessments of arterial blood gases and oxygen saturation may be of great value in diagnosing acute PE in older patients because $P_{aO_2}$ values of less than 80 mm Hg are found in 97% of patients with acute PE who are older than 40 years (127). In contrast, older patients with acute PE often have preexisting lung disease, and 40% of such patients with large matched defects on $V/Q$ scanning results will have acute PE. Caution must be used when administering anticoagulation therapy in older patients. For example, older individuals are at a greater risk of bleeding secondary to warfarin therapy than are other patient subgroups. Therefore, the starting dose should begin at 5 mg or less.
Counseling and Prevention

The most important factor in assessing the risk of venous thromboembolism in a perioperative or pregnant patient with an inherited thrombophilia is her personal and family history of thrombosis (Box 6). Other risk factors also should be taken into consideration (Box 1).

High-Risk Nonpregnant Women Who Do Not Require Surgery

For nonpregnant women at risk of venous thromboembolism who do not require surgery, long-term oral anticoagulation therapy may be indicated (Table 3). For patients not requiring chronic warfarin therapy, aspirin (typically 325 mg) appears to be an inexpensive, well-tolerated, somewhat effective antithrombotic agent. In a meta-analysis of 53 randomized trials in which antiplatelet therapy was used for the prevention of venous thromboembolism either preoperatively or in immobilized patients, it was shown that even a few weeks of antiplatelet therapy reduced the risk of DVT (25% versus 34%) (128). There was an even greater relative reduction in the occurrence of acute PE (1% versus 2.7%). When the analyses were confined to surgical trials, similar reductions were noted in deaths from acute PE (0.9% versus 0.2%; \( P = .0001 \)).

Perioperative and Pregnancy-Related Considerations

Nonpharmacologic Interventions

Nonpharmacologic therapies aimed at preventing venous thromboembolism include graduated elastic compression stockings and pneumatic compression devices. In a Cochrane review of randomized controlled trials, it was indicated that the use of graduated compression stockings in hospitalized patients with prolonged medical immobilization or when applied on the day before surgery or on the day of surgery and worn until

Box 6. Counseling: Establishing a Dialogue

The obstetrician–gynecologist can ask the patient the following questions to help establish her individual risk of venous thromboembolism:

- Have you ever had blood clots in your leg, arm, lung, brain, or any other area of your body?*
- Has any member of your immediate family (i.e., mother, father, sisters, brothers, or children) had such clotting?
- Have you ever been treated for blood clots?
- Have you ever received blood thinners, such as warfarin or coumarin, heparin, or low molecular weight heparin?

*If the patient has had blood clots in the leg or arm, an attempt should be made to differentiate superficial clots from deep venous thrombophlebitis.
discharge or until patients were fully mobile reduced the occurrence of DVT from 21% to 9% (OR, 0.33; 95% CI, 0.26–0.41) (129). Elastic compression stockings also may reduce the occurrence of postphlebitic syndrome after DVT. It was suggested in a cohort study that use of graduated elastic compression stockings in pregnant women reduced the prevalence of postpartum venous thromboembolism from 4.3% to 0.9% (130). However, the efficacy of these devices in pregnancy is uncertain.

Intermittent pneumatic compression devices increase blood flow in the femoral vessels and enhance fibrinolysis by increasing levels of tissue plasminogen activator and decreasing levels of PAI-1. In a meta-analysis in patients at high and moderate risk, it was suggested that the use of intermittent pneumatic compression devices decreased the RR of DVT by 62% compared with placebo, 47% compared with the use of graduated compression stockings, and 48% compared with the use of low-dose unfractionated heparin (131). The author concluded that the use of intermittent pneumatic compression devices decreases the incidence of DVT in patients at moderate to high risk and is probably more efficacious than the use of graduated compression stockings or minidose heparin; however, these devices are not protective against acute PE.

Because the use of graduated elastic compression stockings and pneumatic compression devices poses no hemorrhagic risk and has been shown to be an effective means of DVT prophylaxis in surgical patients and possibly in pregnant patients, they should be strongly considered for prophylaxis in all patients undergoing gynecologic surgery and in pregnant patients at high risk (eg, obese or thrombophilic patients or those with a strong family history of DVT) who require prolonged bed rest as well as in all pregnant patients giving birth by elective cesarean delivery.

Expert panels have recommended that patients at high risk who undergo general surgery receive a combination of both low-dose unfractionated or low molecular weight heparin and use graduated compression stockings, intermittent pneumatic compression devices, or both (19). In pregnancy, left-lateral decubitus positioning during the third trimester also may reduce the risk of venous thromboembolism. Pneumatic compression boots should be used for all patients undergoing cesarean delivery and in the postoperative period until the patients are actively ambulating.

**Pharmacologic Interventions**

**Gynecologic Surgery.** As many as 40% of patients will develop postoperative venous thromboembolism that is detected by sensitive means after gynecologic surgery for malignant disease, whereas up to 10% will do so after gynecologic surgery for benign conditions. Although the use of graduated elastic compression stockings or intermittent pneumatic compression prophylaxis or both generally appears to reduce this risk, it is not eliminated. In a retrospective review of 1,862 consecutive patients who had gynecologic surgery and were treated with intermittent pneumatic compression, an overall incidence of postoperative venous thromboembolism of 1.3% was noted (15 cases of acute PE and 9 cases of DVT) (132). Multivariable regression analysis found that
cancer, a history of prior DVT, and age older than 60 years were independent risk factors for failure of intermittent pneumatic compression to prevent intraoperative venous thromboembolism.

It is important to consider both the risk of venous thromboembolism and the risk of bleeding in choosing the optimal approach to thromboprophylaxis. There are several scoring systems that can be used to assess the risk of thrombosis in women who undergo gynecologic surgery. The Caprini risk assessment tool is relatively easy to use and has been incorporated into the most recent American College of Chest Physicians guidelines (133). After considering the level of risk for thrombosis and hemorrhage, one can then determine the optimal approach for the prevention of venous thromboembolism in patients who undergo gynecologic surgery (133).

Whereas this paradigm seeks to draw a balance between the risk of venous thromboembolism and bleeding caused by heparin prophylaxis, some experts have recommended unfractionated heparin and low molecular weight heparin thromboprophylaxis for all patients undergoing major gynecologic surgery or major, open urologic procedures (133). Individual patient characteristics must be considered in weighing the risk of postoperative hematoma formation against that of perioperative venous thromboembolism when considering perioperative heparin thromboprophylaxis. Heparin prophylaxis ideally is started before surgery and continued until the patient is ambulating. In general surgery, such prophylaxis reduces the incidence of acute PE by sevenfold and DVT by threefold. It is noteworthy that thromboprophylaxis is currently underused in gynecologic surgery (134).

**Pregnancy.** As noted, among pregnant patients who have had a previous venous thromboembolism, recurrence risks are highly dependent on the presence of a thrombophilia and the nature of the risk factors associated with the previous event (80). Thus, such patients should be screened for thrombophilies, and the events surrounding the venous thromboembolism episode should be reviewed in detail. Women with a prior venous thromboembolism associated with a nonrecurring risk factor while not pregnant who have not been exposed to HT and do not have thrombophilia or other current major risk or susceptibility factors (eg, need for prolonged bed rest, obesity, or current superficial thrombophlebitis) do not appear to need antepartum prophylactic heparin therapy during pregnancy. However, they should receive postpartum prophylaxis because most pregnancy-associated fatal cases of acute PE occur in the postpartum period. Conversely, thrombophilic patients with prior venous thromboembolism or those with prior unexplained venous thromboembolism or prior thrombosis while pregnant or receiving exogenous hormones or who have or develop other major risk or susceptibility factors should have both antepartum and postpartum unfractionated heparin or low molecular weight heparin prophylaxis.

Minidose heparin has been effective in preventing DVT in pregnant patients at risk. The standard prophylactic regimen of unfractionated heparin used in pregnancy consists of 5,000 units, administered subcutaneously every 12 hours, increased by 2,500 units in the second and third trimesters. However, some authors recommend monitoring
antifactor Xa levels to guide venous thromboembolism prophylaxis during pregnancy. For example, in one study, it was observed that this standard prophylactic heparin regimen was inadequate to achieve the desired antifactor Xa therapeutic range in 5 of 9 patients with second-trimester pregnancies and in 6 of 13 patients with third-trimester pregnancies (135). In a separate investigation, the authors evaluated whether the standard therapeutic doses of the low molecular weight heparin and dalteparin maintained peak therapeutic levels of anticoagulation during pregnancy (136). Patients received dalteparin, 100 units per kilogram, subcutaneously every 12 hours, and peak and trough (predose) antifactor Xa activity levels were monitored every 2 weeks. Dosage adjustments were made to maintain peak antifactor Xa activity between 0.5 international units per milliliter and 1 international unit per milliliter. The authors noted that 85% (11 of 13) of patients required an upward dosage adjustment. Thus, it appears prudent to monitor antifactor Xa activity for both prophylactic and therapeutic unfractionated heparin and low molecular weight heparin therapy during pregnancy, adjusting the doses to maintain an appropriate prophylactic or therapeutic level 6 hours and 4 hours after an injection, respectively. Another reasonable approach is to use a slightly higher dose in pregnant (compared with nonpregnant) women for thromboprophylaxis without assessing levels of anticoagulation. Examples would be 7,500 units of unfractionated heparin twice daily or 30 mg of enoxaparin twice daily.

Patients with highly thrombogenic thrombophilias (eg, antithrombin deficiency or homozygotes and compound heterozygotes for the factor V Leiden or prothrombin mutations) have a 10-fold higher rate of venous thromboembolism during pregnancy, regardless of personal or family histories (Table 2). Therefore, they should receive unfractionated heparin or low molecular weight heparin therapy during pregnancy and anticoagulation therapy in the puerperium, regardless of their history of prior venous thromboembolism. Such therapy does not appear justified in patients with less thrombogenic thrombophilias (heterozygous factor V Leiden and prothrombin gene mutations and protein C, protein S, and protein Z deficiencies) without a history of venous thromboembolism. However, they should receive postpartum anticoagulation therapy if they require a cesarean delivery or have an affected first-degree family member to reduce the risk of a fatal acute PE (Table 2). Some investigators also recommend antepartum prophylaxis in carriers of lesser thrombogenic mutations who have first-degree family members with venous thromboembolism. Current recommendations regarding antithrombotic therapy and pregnancy are summarized in the most recent guidelines of the American College of Chest Physicians (137). A summary of reasonable approaches to thromboprophylaxis in women with inherited thrombophilias has been presented (138).

Limited studies have assessed the value of routine perioperative thromboprophylaxis with cesarean delivery. As noted, use of graduated elastic compression stockings appears to reduce the prevalence of postpartum venous thromboembolism (130). Intermittent pneumatic compression devices should be used in all patients undergoing cesarean delivery without prior labor. However, perioperative thromboprophylaxis with low-dose unfractionated heparin may be appropriate in patients undergoing cesarean delivery who
have a history of venous thromboembolism, known thrombogenic thrombophilia (Table 2), mechanical heart valve prostheses, and other significant risk factors (137). As with gynecologic surgery, there is considerable room for improvement regarding the optimal use of thromboprophylaxis in women undergoing cesarean delivery (139).

**CASE NO. 6.** A 30-year-old primigravid woman is seen for her first prenatal visit at 8 weeks of gestation. She has an unremarkable medical history. She had been using a diaphragm for contraception for the past year before attempting conception. She was found to be heterozygous for the factor V Leiden mutation when the family was screened after her sister developed an acute PE after hip surgery.

This patient, who is heterozygous for factor V Leiden, has no personal history of thrombosis or of pregnancy loss. She does have an affected first-degree relative, but her sister had thrombosis after a thrombogenic stimulus (ie, hip surgery). Thus, this patient’s risk of thrombosis during pregnancy likely is between 0.2% and 10%. If she has no other risk factors (eg, obesity or subsequent requirement for prolonged immobilization), it is reasonable to offer her no antepartum thromboprophylaxis or antepartum elastic compression stockings and postpartum anticoagulation prophylaxis. If her sister’s thrombotic episode was not associated with a major risk factor, stronger consideration should be given to antepartum prophylaxis.

**Inferior Vena Cava Filters**
Inferior vena cava filters are designed for use in patients in whom anticoagulation therapy is absolutely contraindicated, such as those with a hemorrhagic stroke, recent or current hemorrhage, and recent surgery. Also, they are appropriate in patients with recurrent acute PE, despite adequate anticoagulation therapy, and in those in whom an acute PE would likely be lethal (eg, patients with pulmonary hypertension). Pregnant patients with a history of type 2 heparin-induced thrombocytopenia or allergies to both unfractionated heparin and low molecular weight heparin were traditional candidates for inferior vena cava filters; however, the advent of fondaparinux and direct-thrombin inhibitors has altered this indication. Although their use generally is discouraged in younger patients, retrievable filters have been used successfully in pregnant women and may prove ideal in this setting.

**Pregnant Women With Mechanical Heart Valve Prostheses**
A considerable controversy exists regarding the optimal treatment of pregnant women with mechanical heart valve prostheses who require life-long anticoagulation. Although such patients are treated with warfarin in the nonpregnant state, warfarin is loosely bound to albumin, readily crosses the placenta, and is associated with both an embryopathy and fetopathy. Embryopathy occurs with exposure between 7 weeks of gestation and 12 weeks of gestation and is manifested by nasal hypoplasia, stippled epiphysis, and characteristic central nervous system defects, including agenesis of the corpus callosum, Dandy–Walker syndrome, midline cerebellar atrophy, and ventral midline dysplasia with optic atrophy. Fetal and placental hemorrhage also is a major complication of warfarin
use throughout pregnancy. For these reasons, the agent generally is avoided during pregnancy. However, it may be appropriate to use warfarin in pregnant patients with mechanical heart valves. In a meta-analysis, it was suggested that when warfarin is used throughout pregnancy, the risk of embryopathy is 6.4% (4.6–8.9%) among live births, but this regimen was associated with the lowest risk of valvular thrombosis (3.9%; 2.9–5.9%) (140). In contrast, initiation of heparin at 6 weeks of gestation or through 12 weeks of gestation and its reinitiation after 36 weeks of gestation appears to eliminate fetal risk but is associated with a higher risk of valve thrombosis (9.2%; 5.9–13.9%). Previously, it was thought that dosages of warfarin less than 5 mg/d were associated with decreased risk of embryopathy (141). However, embryopathy may occur at doses less than 5 mg/d (141).

When warfarin is used in this setting, the target INR should be 2.5–3.5. Low-dose aspirin should be used as an adjunct to warfarin based on a study of antithrombotic therapy in patients at high risk with mechanical valves. Warfarin therapy should be stopped by 36 weeks of gestation and either therapeutic unfractionated heparin or low molecular weight heparin should be started to minimize the risk of maternal and fetal hemorrhage during labor and delivery. In this setting, unfractionated heparin doses are adjusted to keep the aPTT at two times the control or an antifactor Xa heparin level of 0.8–1.2 units per milliliter. Doses of low molecular weight heparin should be adjusted according to weight and to keep a 4-hour postinjection antifactor Xa heparin level at approximately 1 unit per milliliter. Because warfarin does not accumulate in breast milk and does not induce an anticoagulant effect in the infant, it is not contraindicated in breastfeeding women.

No large clinical studies exist to guide the use of low molecular weight heparin without warfarin in pregnant patients with mechanical heart valves. However, the manufacturer of enoxaparin specifically recommends against its use in this setting based on a small number of reports to the FDA of valvular thrombosis in pregnant women treated with this agent. However, in 2002, the Anticoagulation in Prosthetic Valves and Pregnancy Consensus Report Panel and Scientific Roundtable analyzed these reported cases of valvular thrombosis in pregnant patients receiving low molecular weight heparin for mechanical heart valve prostheses and concluded that virtually all such cases were associated with underdosage or inadequate monitoring (142). The group recommended enoxaparin therapy in such patients in lieu of warfarin. The starting dosage should be 1 mg/kg, subcutaneously, every 12 hours, with subsequent monitoring of antifactor Xa peak levels 4 hours after injection and also trough levels before the next dose. Dose adjustments are then made to maintain a trough level between 0.5 units per milliliter and 1.2 units per milliliter. In addition, the use of low-dose aspirin was recommended in such patients (142). The authors have used this regimen without thrombosis or adverse fetal sequelae in several cases. These patients should be extensively counseled about the risks and benefits of these different regimens for both their own health and that of their fetuses. Patients so affected may wish to avoid pregnancy altogether because there is a substantial risk no matter what regimen is used. These patients should be managed in cooperation with a cardiologist and hematologist or maternal–fetal medicine specialist or both.
Although it is unclear whether alternative medicines can play a role in the prevention of venous thromboembolism, it appears that they may pose a thrombotic risk. Ephedra was removed from the U.S. marketplace by the FDA because of its link to myocardial infarction. Hops, red clover, soy isoflavone, kudzu, soybean extracts, and various other phytostrogens may increase clotting potential, particularly in patients at risk (143). Box 7 contains a list of herbs and supplements that may interfere with anticoagulant therapy.

**Box 7. Herbs and Supplements That May Interfere With Anticoagulant Therapy**

- Chinese wolfberry
- Coenzyme Q10
- Cranberry juice
- Curbicin
- Danshen
- Devil’s claw
- Dong quai
- Fenugreek
- Garlic
- Ginger
- Ginkgo
- Ginseng
- Glucosamine–chondroitin
- Grapefruit juice
- Green tea
- Melatonin
- Omega-3 fatty acid (fish oil)
- Papaya extract
- Guilinggao
- St. John’s wort

Referral

Most nonpregnant women with new-onset venous thromboembolism receive medical care from internists. However, prevention and early detection often are a part of obstetric–gynecologic care. For patients at high risk of venous thromboembolism who require surgery or in whom estrogen-containing HT is indicated, a consultation with a hematologist may be warranted. For pregnant patients with new-onset acute PE, a consultation with either a maternal–fetal medicine specialist or hematologist should be sought if practicable. Diagnosis and treatment of an uncomplicated DVT and prophylaxis in pregnancy in women with a prior unexplained venous thromboembolism or those with a prior venous thromboembolism who harbor a thrombophilia can reasonably be managed by a general obstetrician–gynecologist.

Key Points

Venous thromboembolism is a leading cause of morbidity and mortality in women (1). Accordingly, obstetrician–gynecologists need to be familiar with risk factors, diagnosis, treatment, and prevention strategies of venous thromboembolism. The key points to keep in mind include the following:

- Most DVT occurs in leg veins.
- Approximately 90% of pulmonary emboli arise from DVT, typically in proximal leg veins (1).
- Women with DVT are at high risk of postphlebitic syndrome.
- Risk of VTE increases with use of exogenous estrogen, pregnancy, and gynecologic surgery.
- Risk of VTE increases up to 10-fold as a result of increased clotting factors, venous stasis, and tissue injury.
- Increased risk of VTE associated with pregnancy persists through 12 weeks postpartum (14).
- Other risk factors for VTE include obesity, increasing age, tobacco use, and comorbid medical conditions, such as cancer.
- Thrombophilias comprise a heterogeneous group of conditions that increase the risk of VTE.
- Antiphospholipid syndrome is the most common acquired thrombophilia. Testing includes lupus anticoagulant screen, anticardiolipin antibody test, and anti-β2-glycoprotein-I antibody test.
- Heritable thrombophilias that obstetrician–gynecologists should be familiar with include the factor V Leiden mutation, the prothrombin gene G20210A mutation, and deficiencies of protein C, protein S, and antithrombin III levels.
• Factor V Leiden mutation is the most common heritable thrombophilia and is associated with activated protein C resistance. It is present in 3–15% of select European populations and 3% of African Americans and is rare in Africans and Asians (31).

• The prothrombin gene mutation is present in 2–5% of Europeans (42). It is associated with an increase in the level of prothrombin, a procoagulant protein.

• Antithrombin III, protein C, and protein S deficiencies are less common than other thrombophilias (affecting less than 1% of individuals) (Table 1 and Table 2).

• Inherited thrombophilias have not been associated with adverse obstetric outcomes in prospective cohort studies, and testing women with obstetric complications is not recommended.

• Women who take unfractionated heparin or therapeutic doses of low molecular weight heparin should be screened for heparin-induced thrombocytopenia.

• Therapeutic unfractionated heparin should yield a heparin level of 0.2–0.4 units per milliliter, an antifactor Xa level of 0.3–0.6 units per milliliter, or an aPTT at 1.5–2.3 times that of a control.

• The dosage of low molecular weight heparin is based on weight. Some authorities propose assessing levels in the setting of obesity, pregnancy, and renal insufficiency. Antifactor Xa levels should be 0.6–1 units per milliliter 4 hours after injection.

• Coumarin should be given to maintain an INR of 2–3.

• Routine screening for thrombophilias before treatment with estrogen therapy is not advised.

• Estrogen therapy should be avoided in women with prior venous thromboembolism.

• Clinical signs and symptoms of DVT are unreliable and are insufficient for establishing a diagnosis.

• Venous ultrasonography is the primary diagnostic modality for DVT.

• D-dimer assays may be useful as a screening test to exclude venous thromboembolism. They are not accurate in pregnant women.

• Both V/Q scanning and CT pulmonary angiography are good primary diagnostic modalities for patients with PE.

• Many factors should be considered when deciding the level and duration of treatment for venous thromboembolism, including the extent and location of the thrombosis, underlying thrombophilias, recurrence, and other risk factors.
Resources

American College of Obstetricians and Gynecologists
ACOG Patient Education Pamphlet - Preventing Deep Vein Thrombosis (AP174, 2010)

Other Resources
The following list is for information purposes only. Referral to these sources and web sites does not imply the endorsement of the American College of Obstetricians and Gynecologists. This list is not meant to be comprehensive. The exclusion of a source or web site does not reflect the quality of that source or web site. Please note that web sites are subject to change without notice.

Publications

Online Resources

Agencies and Organizations
American College of Cardiology
Heart House
2400 N Street, NW
Washington, DC 20037
Telephone: 800-253-4636 or 202-375-6000
Web: www.acc.org
American Heart Association
National Center
7272 Greenville Avenue
Dallas, TX 75231
Telephone: 800-242-8721
Web: www.heart.org/HEARTORG
Agencies and Organizations (continued)
American Society for Metabolic and Bariatric Surgery
100 SW 75th Street, Suite 201
Gainesville, FL 32607
Telephone: 352-331-4900
Web: www.asbs.org

American Thoracic Society
25 Broadway
New York, NY 10004
Telephone: 212-315-8600
Web: www.thoracic.org

Centers for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30329-4027
Telephone: 800-232-4636
Web: www.cdc.gov

Endocrine Society
2055 L Street, NW, Suite 600
Washington, DC 20036
Telephone: 888-363-6274 or 202-971-3636
Web: www.endocrine.org

International Society on Thrombosis and Haemostasis
610 Jones Ferry Road, Suite 205
Carrboro, NC 27510-6113
Telephone: 919-929-3807
Web: www.isth.org

National Heart, Lung, and Blood Institute
PO Box 30105
Bethesda, MD 20824-0105
Telephone: 301-592-8573
Web: www.nhlbi.nih.gov

The Association for the Study of Obesity
4 Bank Court, Weldon Road
Loughborough, LE11 5RF
United Kingdom
Telephone: 44-0-7448-288485
Web: www.aso.org.uk

The Obesity Society
1110 Bonifant Street, Suite 500
Silver Spring, MD 20910
Telephone: 301-563-6526
Web: www.obesity.org

Vascular Cures
555 Price Avenue, Suite 81
Redwood City, CA 94063
Telephone: 650-368-6022
Web: vascularcures.org
Test Your Clinical Skills

Complete the answer sheet at www.clinicalupdates.org under “Test Your Clinical Skills” and receive 5 continuing medical education credits. The answers appear on page 69.

Directions: Select the one best answer or completion.

1. The most active inhibitor of thrombin is
   A. antithrombin
   B. protein C
   C. protein S
   D. protein Z

2. In a pregnant woman at 29 weeks of gestation, venous flow velocity in the legs decreases by
   A. 10%
   B. 25%
   C. 50%
   D. 75%

3. Most pregnancy losses in patients with antiphospholipid antibodies occur at what gestational age?
   A. Before 10 weeks
   B. After 10 weeks
   C. After 20 weeks
   D. After 30 weeks

4. A patient in 39th week of gestation has a new diagnosis of deep vein thrombosis. She desires epidural anesthesia when in labor. The best choice for anticoagulation is
   A. dalteparin
   B. enoxaprin
   C. fondaparinux
   D. heparin

5. The best agent to use for anticoagulation perioperatively in a patient with heparin-induced thrombocytopenia is
   A. dalteparin
   B. enoxaprin
   C. fondaparinux
   D. bivalirudin

6. Carriers of factor V Leiden taking oral contraceptives have how many times the risk of thromboembolism compared with women who are not carriers but are also taking oral contraceptives?
   A. 2
   B. 3
   C. 5
   D. 7

7. The authors cite a study reporting a 3-year fatality rate after acute PE of
   A. 12%
   B. 30%
   C. 75%
   D. 90%
8. The main criterion for diagnosing venous thrombosis by ultrasonography is
   A. compressibility of vein lumen
   B. distention of vein lumen
   C. reduced amount of blood flow in proximal portion of vein
   D. reduced velocity of blood flow in distal portion of vein

9. In a patient with acute PE, which of the following findings on chest X-ray is least commonly seen?
   A. Atelectasis
   B. Decreased vascularity
   C. Elevated hemidiaphragm
   D. Pleural effusion

10. Compared with the diagnostic workup of acute PE in nonpregnant patients, which of the following tests is less useful in the diagnostic workup of pregnant patients?
    A. Chest X-ray
    B. CT pulmonary angiogram
    C. D-dimer
    D. V/Q scan

11. When monitoring low molecular weight heparin dosage using antifactor Xa levels, the desirable level for therapeutic doses is how many fold the desirable level for prophylactic doses?
    A. 1
    B. 2
    C. 3
    D. 5

12. In a meta-analysis of risk of DVT in surgical patients, which of the following showed the greatest reduction in risk?
    A. Graduated compression stockings
    B. Intermittent pneumatic compression device
    C. Low-dose low molecular weight heparin
    D. Low-dose unfractionated heparin

13. When do most pregnancy-associated fatal cases of acute PE occur?
    A. In the first trimester
    B. In the second trimester
    C. In the third trimester
    D. In the postpartum period

14. According to the authors, which of the following patients should not be managed solely by the general obstetrician–gynecologist?
    A. Nonpregnant patient at high risk of venous thromboembolism in whom estrogen-containing HT is indicated
    B. Pregnant patient with uncomplicated DVT
    C. Pregnant patient with prior unexplained venous thromboembolism
    D. Pregnant patient with thrombophilia and prior venous thromboembolism


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Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Answers

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