Thromboembolism in Pregnancy

Victor A. Rosenberg, MD*, Charles J. Lockwood, MD

*Department of Obstetrics, Gynecology and Reproductive Sciences,
Yale University School of Medicine, 333 Cedar Street,
PO Box 208063, New Haven, CT 06520, USA*

Of the potential clinical emergencies an obstetrician/gynecologist will confront, venous thromboembolism, which includes deep venous thrombosis and pulmonary embolus, has been associated with the highest risk for maternal and fetal morbidity and mortality. In the most recent Centers for Disease Control and Prevention data available, thromboembolism was shown to be responsible for 19.6% of pregnancy-related deaths in the United States as compared with 17.2% for hemorrhage [1]. Venous thromboembolism is estimated to complicate between 0.5 and 1 in 1000 pregnancies per year in the United States [2–10]. More recent evidence suggests that the risk is evenly divided among each of the trimesters [3,11], with an even higher risk in the postpartum period [12,13]. In addition, cesarean delivery confers a five- to ninefold higher risk over vaginal delivery [13,14].

Essentially, every pregnant patient is at risk for a venous thromboembolic event and the risk is estimated to be five- to 10-fold higher than for the nonpregnant patient. From a teleological perspective, the adaptation of the maternal hemostatic system to pregnancy (to prevent hemorrhage at the time of delivery) predisposes women to an increased risk of thromboembolism. Particular women seem to be at yet an even higher risk for venous thromboembolism in pregnancy. These women include multiparous patients, obese gravidas, women who have postpartum endometritis, and those with a history of venous thromboembolism or underlying thrombophilia. It is estimated that the recurrence risk in pregnancy is between 5% and 16% for women with a history of a venous thromboembolism [11,15] and may be related to the presence or absence of underlying maternal thrombophilia [16]. Others have demonstrated a 7.5% recurrence risk in pregnancy if the first venous thromboembolism was unprovoked, related to pregnancy, or related to use of oral contraceptives [17]. In contrast, there

* Corresponding author.
E-mail address: victor.rosenberg@yale.edu (V.A. Rosenberg).

was no recurrence if the first venous thromboembolism was related to other transient risk factors [17]. Therefore, one must consider routine thromboprophylaxis in selected obstetrical patients [15,17–19].

However, despite prophylaxis, venous thromboembolism can occur in pregnancy and clinicians must have a heightened surveillance for this potential emergency. Diagnostic tests must be readily available and there should be no delay in initiating treatment when appropriate [20]. Treatment goals should include preclusion of further thrombus propagation and pulmonary embolism and prevention of recurrent venous thromboembolism and long-term complications, including venous insufficiency, pulmonary hypertension, right-sided heart failure, and "post-thrombotic syndrome" [21].

This article focuses on the clinical emergency posed by deep venous thrombosis and pulmonary embolism in pregnancy. The article begins with a brief review of the physiologic changes that predispose pregnant women to a thrombotic event. The article then reviews the signs and symptoms that should alert the clinician to the possibility of a thromboembolic event, and then presents an algorithm outlining specific diagnostic tests that guide the clinician to the correct diagnosis. The article then reviews recommended treatment regimens while attempting to resolve some of the controversies regarding optimal anticoagulation therapy in pregnancy. The article ends with a brief look at future directions, including innovative diagnostic tests that may be safer and easier to perform than current ones.

Physiology and pathophysiology of hemostasis in pregnancy

The adaptation of the maternal hemostatic system to pregnancy predisposes women to an increased risk of venous thromboembolism. Pregnancy produces the components of Virchow's triad, including an increase in vascular stasis, changes in the coagulation system, and vascular injury. Other risk factors for thrombosis involve inherited thrombophilias, including mutations in the factor V Leiden and prothrombin genes; deficiencies in protein C, protein S, and antithrombin III; and acquired maternal thrombophilias, such as the condition known as antiphospholipid antibody syndrome [12,22,23]. It is estimated that an underlying thrombophilia is present in at least 50% of those who develop a deep venous thrombosis or pulmonary embolism in pregnancy [23]. Therefore, a thorough understanding of the coagulation and fibrinolytic systems and their inhibitors with specific relation to pregnancy is essential.

Physiology

Platelet aggregation and vasoconstriction are the initial responses to hemorrhage following vascular disruption and endothelial damage. By limiting the size of the requisite plug required to obstruct blood flow through the vascular defect, vasoconstriction limits blood flow to promote platelet

plug formation. Integrins bound to platelet membranes adhere to subendothelial laminin, fibronectin, and vitronectin, and circulating von Willebrand's factor mediates platelet attachment by binding to both platelet GPIb/IX/V receptors and subendothelial collagen in damaged vessels [24]. Platelet adhesion then triggers calcium-dependent protein kinase C activation, which induces thromboxane A2 (TXA2) synthesis and platelet granule release. The α-granules contain von Willebrand's factor and various clotting factors while dense-granules contain adenosine diphosphate and serotonin, which together with thromboxane A2 (TXA2), exacerbate vasoconstriction and platelet activation. The latter process activates platelet GPIIB/IIIa receptors to promote aggregation by forming inter-platelet fibrinogen, fibronectin, and vitronectin bridges [25]. Epinephrine, arachidonic acid, and platelet activating factor can also activate platelets.

Tissue factor, a glycoprotein bound to cell membranes, is the primary initiator of hemostasis and the coagulation cascade. Tissue factor is expressed constitutively by epithelial, stromal, and perivascular cells throughout the body. Tissue factor is also expressed, particularly in pregnancy, in endometrial stromal cells and uterine decidua [26,27]. Clotting is initiated by the binding of tissue factor to factor VII after vascular injury and can be externally activated by thrombin, factor IXa, factor Xa, or factor XIIa [26,27]. The coagulation cascade is initiated and, ultimately, thrombin cleaves fibrinogen to fibrin monomers, which self-polymerize and are cross-linked via thrombin-activated factor XIIIa.

The counterpoise of the hemostatic system is the anticoagulant system. The tissue factor pathway inhibitor is the first agent in this system and acts on the factor-Xa–tissue factor–factor-VIIa complex to inhibit tissue-factor–mediated clotting [28]. However, factor XIa can bypass this block and sustain clotting for some time. As a result, additional endogenous anticoagulant molecules are required to avoid thrombosis, including activated protein C, protein S, and protein Z.

Fibrinolysis is initiated by tissue-type plasminogen activator (tPA), which cleaves plasminogen to generate plasmin. Plasmin, in turn, cleaves fibrin into fibrin degradation products (FDPs). These FDPs can also inhibit thrombin action, a favorable result when limited, but when generated in excess can contribute to disseminated intravascular coagulation. Inhibitors of fibrinolysis include α-2-plasmin inhibitor and type-1 and -2 plasminogen activator inhibitors (PAI-1 and -2), which inactivate tPA. The endothelium and uterine decidua are primary sources of PAI-1, while the placenta produces PAI-2 [29]. The thrombin-activatable fibrinolysis inhibitor modifies fibrin to render it resistant to inactivation by plasmin [30].

Pathophysiology

Changes in decidual and systemic hemostatic systems occur in pregnancy, likely to meet the hemorrhagic challenges poised by implantation,

placentation, and the third stage of labor. Decidual tissue factor and PAI-1 expression increase in response to progesterone, providing a potent local system of hemostasis to prevent hemorrhage. In addition, levels of placental PAI-2, circulating levels of fibrinogen, and levels of factors VII, VIII, IX, X, and XII and of von Willebrand's factor increase considerably in gestation [29–32]. While these mechanisms serve to generally prevent puerperal hemorrhage following significant uterine vascular trauma at the time of delivery, they predispose to thrombosis, a tendency aggravated by maternal thrombophilias.

Inherited thrombophilias refer to a genetic tendency to venous thromboembolism. Disorders include the factor V Leiden and prothrombin gene G20210A mutations, antithrombin deficiency, and protein C and S deficiencies. Acquired thrombophilias include the antiphospholipid antibody syndrome, which is characterized by the presence of antibodies directed against plasma proteins bound to anionic phospholipids.

The antiphospholipid antibody syndrome is responsible for 14% of venous thromboembolism in pregnancy [33,34]. The lifetime prevalence of arterial or venous thrombosis is approximately 30%, with an event rate of 1% per year [35]. The risks of venous thromboembolism are highly dependent upon the presence of other predisposing factors, including pregnancy, estrogen exposure, surgery, and infection. There is a 5% risk of a thrombotic event in pregnancy even with prophylaxis [36].

The inherited thrombophilias are a heterogeneous group of genetic disorders often associated with a personal or family history of venous thromboembolism. Such a history is an important modifier of projected risk. Thrombophilias are divided into high-risk thrombophilias and low-risk thrombophilias based on the overall risk of venous thromboembolism. Because of the association between thrombophilias and recurrent venous thromboembolism in pregnancy, the authors routinely obtain a comprehensive thrombophilia evaluation on patients diagnosed with venous thromboembolism in pregnancy. However, because functional levels of protein C, protein S, and antithrombin are altered in pregnancy, abnormally low levels should be confirmed 6 weeks postpartum before a diagnosis of a deficiency is made.

Diagnosis of deep vein thrombosis

Clinicians must have a high baseline index for suspicion of deep venous thrombosis in pregnancy because many of the common clinical signs and symptoms, such as lower extremity edema, are also common findings in normal pregnancy. A timely diagnosis of deep venous thrombosis is crucial because up to 24% of patients with untreated deep venous thrombosis will develop a pulmonary embolism [37]. A life-threatening pulmonary embolism usually originates from a clot in the deep veins of the pelvis and legs, including the internal iliac, femoral, and popliteal veins [7].

Common clinical features of deep venous thrombosis include lower extremity edema, pain, difficulty with ambulation, warmth, and erythema. However, the diagnostic sensitivity of these clinical signs and symptoms is at best 50% and the diagnosis of deep venous thrombosis is confirmed in less than a third of patients with these complaints [38,39]. Therefore, patients who present with any of these complaints warrant a full diagnostic workup. Diagnostic tests for evaluation of suspected deep venous thrombosis include D-dimer assays, venous color Doppler ultrasound, magnetic resonance venography, CT, and, less commonly, contrast venography [40,41].

D-dimer assays

D-dimer assay testing may be used as a screening test and/or in combination with venous ultrasound to facilitate diagnosis and prediction of a thromboembolic event. D-dimer is a product of the degradation of fibrin by plasmin. Therefore, elevated levels indicate increased thrombin activity and increased fibrinolysis following fibrin formation [42]. The assay employs monoclonal antibodies to detect D-dimer fragments. Commercial assays available include at least three accurate and reliable products: two rapid enzyme lined immunosorbent assays and a rapid whole-blood assay.

Though quite reliable in the exclusion of deep venous thrombosis in the nonpregnant patient [43,44], the value of D-dimer testing in pregnancy is somewhat controversial because D-dimer levels increase with gestational age and, in the postpartum period, even in the absence of venous thromboembolism [45–48]. This makes it difficult to assign a ''normal'' cutoff. Most studies report a sensitivity ranging from 85% to 97% but a specificity of only 35% to 45% [21,49]. In addition, there appears to be a wide variation in D-dimer assay results depending on the specific test used. These factors have led some investigators to conclude that the literature does not support the general use of D-dimer assays as a stand-alone test for the diagnosis of deep venous thrombosis in pregnancy [50]. However, others argue that D-dimer testing is likely to have a higher negative predictive value in pregnancy and therefore it has a role in the initial triage of patients with suspected deep venous thrombosis. In patients with a negative D-dimer assay and a low clinical probability of deep venous thrombosis, further testing may be unnecessary (Fig. 1). Several elaborate scoring systems (not validated in pregnancy) have been proposed to help classify patients as either low or high risk for deep venous thrombosis [51,52]. Another approach is to categorize patients as low risk if there is another reasonable clinical explanation for their symptoms and there are no major risk factors, such as recent major abdominal surgery, late pregnancy and postpartum, varicose veins, malignancy, and reduced mobility [53]. In addition, there may be a role for D-dimer testing to identify women at high risk for recurrent venous thrombosis [42].
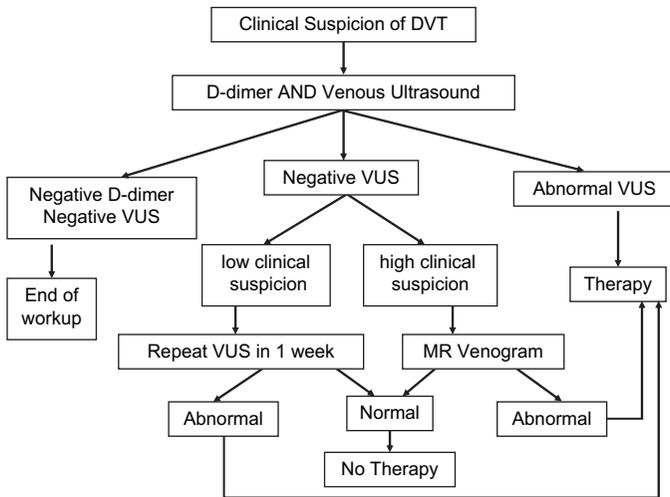
Fig. 1. Diagnostic algorithm for deep venous thrombosis. DVT, deep venous thrombosis; MR, magnetic resonance; VUS, venous ultrasound.

Venous ultrasound

Compression ultrasound aided by color flow Doppler imaging involves the use of firm pressure applied to the ultrasound transducer to detect an intraluminal filling defect of the major venous systems of the legs, including the common femoral, superficial femoral, greater saphenous, and popliteal veins. Noncompressibility of the venous lumen is the most accurate ultrasound criteria for thrombosis [38]. Venous ultrasound to detect deep venous thrombosis has been well studied in pregnancy [54]. It is noninvasive, easy to perform, and can be repeated if necessary without any restrictions. Sensitivity and specificity of venous ultrasound in the detection of proximal deep venous thrombosis is estimated at 95% and 96%, respectively [41,55]. There is a slightly lower sensitivity (75%–90%) in detecting more distal thrombosis in the leg [41,56].

Other modalities

It is estimated that in up to 3% of patients, venous ultrasound is not technically possible [57], and in some patients, despite negative ultrasound results, clinical suspicion remains high. Magnetic resonance venography and CT of the pelvis and lower extremities may be a viable alternative in these patients. Magnetic resonance direct thrombus imaging was shown in a blinded study of nonpregnant patients to have a sensitivity of 94% to 96% and specificity of 90% to 92% for the detection of deep venous thrombosis with similar results for calf deep venous thrombosis. MRI was well tolerated and interpretation was highly reproducible [58–60]. The reported

experience with MRI as a diagnostic modality for pregnant patients with deep venous thrombosis is extremely limited [61] and there is only limited safety data [62]. Thus, while magnetic resonance venography is promising, additional studies are needed before it can be routinely recommended. In the nonpregnant patient, CT of the pelvis and lower extremities to diagnose deep venous thrombosis is a useful modality with a reported sensitivity and specificity similar to ultrasound [63–65]. However, there is no reported experience with this modality in pregnancy and the natural preference during gestation is to test with ultrasound, which does not involve a risk of radiation exposure to the fetus.

Contrast venography involves the injection of radio-opaque dye into the vein below the site of the suspected thrombus. Imaging is then used to identify a filling defect [66]. However, the relative ease and noninvasive nature of compression ultrasound has made this more invasive test somewhat obsolete [21].

Workup of patients with suspected deep venous thrombosis

A diagnostic algorithm is presented in Fig. 1 to guide the clinician in the workup of a pregnant patient with a suspected deep venous thrombosis.

Diagnosis of pulmonary embolus

Timely diagnosis of pulmonary embolus in pregnancy is critical because of the potential for a catastrophic maternal and fetal outcome if overlooked. If the clinical suspicion is high, consideration should be given to empiric anticoagulation until the workup is completed [7]. Likewise, a precise diagnosis is vital to prevent unnecessary treatment of pulmonary embolism because treatment is associated with side effects for both the mother and fetus. Accurate imaging is essential, but fetal radiation exposure during diagnostic procedures often provokes unfounded anxiety for the clinicians involved [67].

An array of clinical, biochemical, and radiological tests is available to aid in the investigation of pulmonary embolism in pregnancy. Because, according to estimates, 70% of patients with proven pulmonary embolism have a proximal deep venous thrombosis, the basic workup begins with compression venous ultrasound if there are any signs or symptoms of thrombosis of the lower extremities. If a deep venous thrombosis is confirmed, then pulmonary embolism can be assumed, and treatment can be initiated without further workup [7,68]. If venous ultrasound is nondiagnostic or not performed, traditional teaching (based on older research) focused on the ventilation–perfusion (VQ) scan as the primary modality to diagnose pulmonary embolism in pregnancy. However, more recent studies support CT pulmonary angiography (CTPA) as the favored diagnostic tool. In fact, the most recent guidelines from the British Thoracic Society recommend CTPA as the initial

lung imaging modality in pregnancy for nonmassive pulonary embolism [53].

Clinical signs and symptoms

Traditional clinical hallmarks of pulmonary embolism, including dyspnea, tachycardia, tachypnea, pleuritic chest pain, and syncope or near-syncope are present in up to 90% of patients found to have a pulmonary embolus. However, these clinical signs and symptoms lack specificity and generate a broad differential diagnosis [69,70]. Other more objective measures, such as low oxygen saturation on pulse oximetry, abnormal arterial blood gas (ABG), abnormal chest radiograph, abnormal EKG, and abnormal echocardiogram, have also been proposed.

Low oxygen saturation on pulse oximetry or ABG has a limited role in the assessment of pregnant patients with suspected pulmonary embolism. These tests are useful in elderly populations, but lack diagnostic accuracy in younger patients, including pregnant patients [71]. Studies have shown that up to 20% of patients with a documented pulmonary embolism, had PO_2 measurements on ABG greater than 85 mm Hg [70]. The alveolar-arterial gradient may be a more sensitive indicator of pulmonary embolism in nonpregnant patients with 86% of patients with documented pulmonary embolism having an alveolar-arterial gradient greater than 20 [70]. However, 58% of pregnant women with documented pulmonary embolism had a normal alveolar-arterial gradient [72].

Abnormalities on EKG, including the classic S1-Q3-T3 changes, may be present in 70% to 90% of patients with pulmonary embolism but are considered nonspecific findings [73,74]. Other EKG findings, such as new-onset atrial fibrillation and right bundle branch block or right axis deviation, are typically later findings after pulmonary embolism and are more suggestive of significant cardiopulmonary compromise. Absence of abnormal EKG findings should not reassure a clinician who has a reasonable suspicion of pulmonary embolism [75].

Initial imaging modalities

The chest radiograph may be abnormal in up to 85% of affected patients. Common findings include effusions, infiltrates, and atelectasis. The ''classic'' wedge-shaped infiltrate (Hampton's hump) or decreased vascularity (Westermark's sign) are, in fact, rare findings [70,76]. Chest radiograph may be helpful in excluding other competing diagnoses, including pneumonia, pulmonary edema, pleural effusions, and pneumothorax.

Echocardiographic abnormalities of right ventricular size and function are present in a significant number of patients with acute large pulmonary embolism. Typical findings include a dilated and hypokinetic right ventricle and tricuspid regurgitation. Transesophageal imaging may enhance diagnostic accuracy [77–79]. A recent observation is that the release of cardiac

troponins can detect acute right heart strain from right ventricular muscle damage in major pulmonary embolism. However, the role of cardiac troponins in decision-making is limited and they are of no diagnostic value in nonmassive pulmonary embolism [80–83].

D-dimer

As with the evaluation of patients with suspected deep venous thrombosis, D-dimer is a sensitive, but not specific test for pulmonary embolism. In nonpregnant patients, a negative D-dimer has a negative predictive value of 95%, but only a 25% specificity [76]. However, as mentioned previously in the discussion regarding the diagnosis of deep venous thrombosis, abnormal cutoffs are difficult to assign in pregnancy because D-dimer levels increase with gestational age, and in the postpartum period, even in the absence of venous thromboembolism [45–48]. A negative D-dimer probably has a role in the exclusion of pulmonary embolism in patients with a low clinical suspicion (see description of risk assessment above), but the assay should not be performed in those with high clinical probability of pulmonary embolism [53].

Pulmonary angiogram

For many years the "gold standard" in diagnosing an acute pulmonary embolism was pulmonary arteriography. Sensitivity approaches 100%, though the ability to detect segmental and subsegmental lesions is considered diminished. The procedure involves catheterization of the pulmonary artery via a femoral or internal jugular approach and noting a filling defect via radiograph or fluoroscopy. This procedure carries significant risk, including 0.5% mortality risk and 3% complication rate, primarily due to the risks of contrast injection and catheter placement. Complications include groin hematoma, cardiac perforation, renal failure, and respiratory failure [69,84–86]. This apparent potential for morbidity led to an intensive effort over the past several years to identify a diagnostic modality that would be safer and easier to perform without sacrificing sensitivity.

Ventilation–perfusion scan

VQ imaging is a well-established diagnostic modality in the workup of a suspected pulmonary embolus in pregnancy and for many years it was the most frequently employed test in this subgroup of patients [67]. The test involves comparative imaging of the pulmonary vascular beds and airspaces using radiolabeled markers injected intravenously and as inhaled gases. Patients are then categorized into different diagnostic probability categories, including low, intermediate, high, normal, and indeterminate [38]. Any outcome other than high probability or normal requires further testing. Radiation dose can be minimized in pregnancy by using a half-dose perfusion scan and only using ventilation imaging if the perfusion scan is

abnormal [87]. Unfortunately, VQ scans are time-consuming and the sensitivity varies widely depending on the degree of clinical suspicion [7].

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study looked at the diagnostic accuracy of VQ scans in nearly 1000 nonpregnant patients with suspected pulmonary embolism. High-probability VQ scans correlated with pulmonary embolism in 87.2% of cases. However, only 41% of patients with pulmonary embolism had high-probability scans, yielding a sensitivity of 41% and a specificity of 97% [74]. In addition, it is estimated that over 10% of patients with a low-probability scan were found to have a pulmonary embolus on subsequent imaging. In the largest published study of VQ scans in pregnancy [68], fewer than 5% of pregnant patients had high-probability scans, almost 25% had indeterminate scans that required further evaluation, and more than 70% had normal scans. This is quite different than in the nonpregnant population where 40% to 70% of scans are nondiagnostic [67].

CT pulmonary angiography

CTPA employs intravenous contrast injection to highlight the pulmonary vasculature while using the latest generation of fast multislice scanners [53,76]. Much of the reluctance to use CTPA in pregnancy revolves around potential radiation exposure to the fetus. In fact, the authors' radiology colleagues often cite unfounded concerns regarding radiation exposure as a reason to refuse to perform CT scan and to promote VQ as the primary imaging modality.

In a recent study, Winer-Muram and colleagues [88] calculated the mean fetal radiation dose from helical chest CT by using maternal–fetal geometries obtained from healthy pregnant women and comparing the calculated CT doses with the doses reported with VQ scan. They found that the average fetal radiation dose is higher with VQ scan than with CT scan in all trimesters of pregnancy. As a corollary, in a survey of health professionals to determine their knowledge of dosimetry in the workup of pulmonary embolism, only 58% appreciated correctly that a VQ scan delivers a higher fetal dose of radiation than that delivered by CT pulmonary angiography [89]. Interestingly, the survey population included medical trainees, radiologists, nuclear physicians, medical physicists, and pulmonologists. Lastly, in a survey of the PIOPED II investigators, only 31% recommended CT as the primary imaging test [90], but 75% of respondents in a conflicting study use CT angiography in pregnant patients [91].

CTPA is a well-validated diagnostic modality with a sensitivity and specificity between 94% and 100%. In a systematic review of available studies, the negative likelihood ratio of pulmonary embolism (pulmonary embolism confirmed by additional imaging) after a negative or inconclusive CT was 0.07; and the negative predictive value was 99.1%. The investigators conclude that the clinical validity of CTPA to diagnose pulmonary embolism

is similar to the clinical validity of pulmonary angiography [92], and missed diagnoses are rare [93]. Others have suggested that in patients with a low clinical suspicion of pulmonary embolism, CTPA has a greater discriminatory power than VQ scanning, but in patients with a high clinical suspicion, CTPA and VQ scan perform similarly [94].

CT is not only safe during pregnancy but also accurate for the diagnosis of pulmonary embolism in main, lobar, and segmental pulmonary arteries [88]. The latest CT technology and techniques are more accurate than VQ technology in identifying peripheral thrombus [53]. CT was also found to be the most cost-effective modality in diagnosing pulmonary embolism in pregnancy with a cost of $17,208 per life saved, compared with $35,906 per life saved for a VQ scan [95].

Given the safety data presented above and the relative ease in obtaining a CT versus a VQ scan, the authors prefer CTPA as the initial diagnostic approach to suspected pulmonary embolism in pregnancy. CTPA is easier to perform, is readily available even in off hours, and rarely requires any follow-up imaging. In fact, many radiology departments have sufficient confidence in the sensitivity of their CT imaging to also forgo formal contrast pulmonary angiography. Another advantage to CT over VQ scan is the ability to detect other disorders that may be responsible for the patient's symptoms, including pulmonary edema, pneumonia (consolidation), and pleural effusions [53].

Magnetic resonance angiography

Magnetic resonance angiography (MRA) uses gadolinium injection during magnetic resonance scanning to visualize the pulmonary vasculature. Newer generation MRI with faster imaging acquisition times have enabled the use of this technique. While initial studies were promising with reportedly high sensitivity and specificity [96], in a prospective study of 141 patients with suspected pulmonary embolism, the overall sensitivity was only 77% when compared with pulmonary angiography [97]. Still, others have proposed a combination of chest MRI and lower extremity magnetic resonance venogram as a way to detect 13% more cases of thromboembolism [98]. Unfortunately, no reported studies have examined the use of magnetic resonance to diagnose pulmonary embolism in pregnancy.

Workup of patients with suspected pulmonary embolism

A diagnostic algorithm is presented in Fig. 2 to guide the clinician in the workup of a pregnant patient with a suspected pulmonary embolism.

Treatment of venous thromboembolism in pregnancy

Whether manifested as a deep venous thrombosis or pulmonary embolism, acute venous thromboembolism in pregnancy requires immediate medical therapy. Initial steps in the management of pulmonary embolism
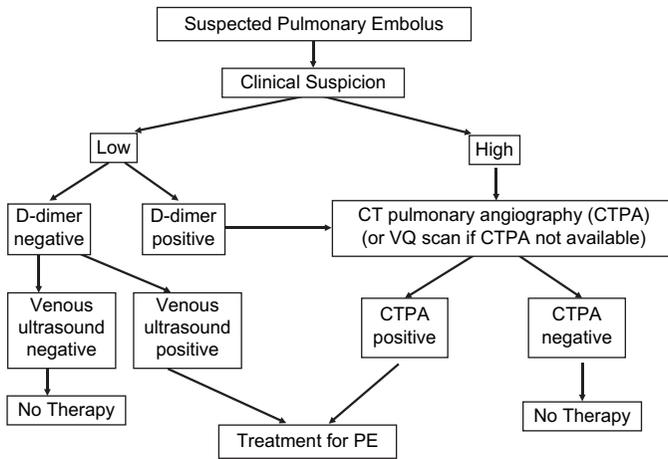
Fig. 2. Diagnostic algorithm for pulmonary embolism. PE, pulmonary embolism.

include oxygen support, blood pressure stabilization, and an assessment of the patient's cardiovascular and respiratory status [7,53]. Consultation with the intensive care unit service may be appropriate and transfer to the intensive care unit should be considered, depending on nursing and physician resources in the unit where the patient is located. Close monitoring for evidence of right-sided cardiac failure in cases of massive pulmonary emboli is warranted [53].

The mainstay of medical treatment is anticoagulation. While conventional treatment recommendations called for unfractionated heparin as the suggested therapy in pregnancy, low molecular weight heparin (LMWH) has emerged as the superior alternative based on more recent studies. Warfarin is seldom a treatment for acute venous thromboembolism in pregnancy given the drug's risk of teratogenicity [20,53], though this risk is greatest between the sixth and 12th weeks of pregnancy. There is also a risk for fetal hemorrhage with warfarin use.

Unfractionated heparin

Unfractionated heparin promotes anticoagulation by inhibiting platelet aggregation and by enhancing and increasing antithrombin and factor Xa inhibitor activity [99]. The initial bolus dose and maintenance dosing are calculated and titrated to achieve an activated partial thromboplastin time (aPTT) at 1.5- to two-times normal [18,99,100]. Standard nomograms are readily available from hospital pharmacies. Once therapeutic dosing is achieved, the aPTT must be periodically monitored to confirm adequate dosing. The potential side effects from unfractionated heparin include hemorrhage, osteoporosis, and thrombocytopenia.

Osteoporosis, or clinically significant bone loss, has been traditionally quoted as an adverse effect of long-term anticoagulation with heparin during pregnancy. Dahlman [101] reported that the incidence of vertebral fractures in 184 women treated with unfractionated heparin during pregnancy was 2.2%. Additionally, the mean duration of heparin prophylaxis in the women who had osteoporosis and spinal fracture was only 17 weeks (range: 7–27 weeks).

Heparin-induced thrombocytopenia (HIT) occurs in approximately 3% of patients receiving unfractionated heparin. Type I, or the immediate form, occurs within days of exposure and is typically self-limited. Type II, the immunoglobulin type, is rare and usually occurs 5 to 14 days after the initiation of therapy [102]. The authors therefore typically monitor platelet counts as follows: complete blood cell count on day 3, then on each of days 7 through 10, and then monthly after starting anticoagulation. A 50% decline in platelet count from the pretreatment level suggests a type II reaction and is an indication to promptly discontinue the heparin. Consultation with hematology would then be recommended for acceptable alternative therapies.

The cumbersome dosing requirements, the need for frequent aPTT monitoring, the need for long-term hospitalization, and concerns regarding side effects, including osteoporosis, osteopenia, and HIT, have led many authorities to recommend LMWH as the primary anticoagulation in pregnancy (see below) [20,53]. However, in certain rare circumstances, the authors prefer unfractionated heparin over LMWH. These include circumstances involving patients who are hemodynamically unstable due to massive pulmonary embolism [53], patients at significant risk for bleeding (eg, immediately postoperation patients or patients with antepartum placental abnormalities), and patients close to term who may require regional anesthesia and/or cesarean delivery. These patients are potentially better served by unfractionated heparin because of its shorter half-life and ease of reversibility with such agents as protamine sulfate. Protamine can be given as an intravenous infusion and dosing is based on residual circulating heparin.

Low molecular weight heparin

LMWHs, including enoxaparin and dalteparin, have established safety profiles in pregnancy and are emerging as the anticoagulant of choice for many indications, including acute venous thromboembolism [20,53,103–107]. LMWHs have potential advantages over unfractionated heparin because they have a lower incidence of HIT [102], a more predictable dose response, and a lower incidence of bone loss related to use. Shefras and colleagues [108] performed serial bone mineral density measurements in women treated with LMWH during pregnancy. Mean bone loss was 5.6% and 5.1%, depending on the dose, but this was not statistically different from the mean bone loss in the control group of pregnant patients who

were not exposed to LMWH (3.1%). In a randomized open study of unfractionated heparin versus LMWH in pregnancy, Pettila [109] showed that bone mineral density, as measured by serial dual energy x-ray absorptiometry scan up to 3 years postpartum, was significantly lower in the unfractionated heparin group versus the LMWH group. However, there was no difference between the LMWH group and healthy controls that were not exposed to heparin therapy.

Many studies have examined the efficacy of LMWH versus unfractionated heparin. In a prospective observational study, Rodie and colleagues [110] demonstrated the safety of enoxaparin for the treatment of acute venous thromboembolism in pregnancy. Few patients needed modification of the initial dose to maintain a therapeutic anti-Xa activity. Jacobson and associates [104] found similar results, but suggested that approximately 10% to 20% higher doses of LMWH may be needed in pregnancy. In a meta-analysis of 11 randomized trials comparing LMWH to unfractionated heparin [103], LMWH reduced mortality rates over 3 to 6 months of patient follow-up (odds ratio: 0.71), had favorable results with regard to major bleeding complications, and had equivalent efficacy to unfractionated heparin in preventing thromboembolic recurrences. Other reviews [106,111] have had similar conclusions. In a decision model, Gould and colleagues reported (in nonpregnant patients) LMWH to be more cost-effective than unfractionated heparin in the treatment of acute deep venous thrombosis [112].

One controversial area with regard to the use of LMWH in pregnancy is the necessity to monitor therapeutic levels (ie, anti-Xa levels). In nonpregnant patients, monitoring is generally not required because anticoagulant effects are predictable [111]. However, in pregnancy, the increased glomerular filtration rate in the kidney may explain the apparent need for increased dosing to maintain therapeutic levels reported in the literature [113]. In addition, there is a greater variability with regard to binding, distribution, and metabolism of LMWH in pregnancy.

The authors' preferred treatment for acute venous thromboembolism in pregnancy is LMWH. Though some have proposed outpatient therapy as a viable option outside of pregnancy [114], initial hospitalization is recommended in a gravid patient. The authors start with enoxaparin at a dose of 1 mg/kg subcutaneously given twice a day. The authors typically follow anti-Xa levels monthly and adjust the LMWH dosing to achieve a peak anti-Xa level of 0.6 to 1.0 U/mL (3–4 hours after injection). The authors also prefer twice-daily over once-daily dosing. It is recommended to continue therapeutic anticoagulation for at least 20 weeks. If this period expires before the end of pregnancy or the postpartum period, prophylactic anticoagulation should be initiated unless the patient has another indication for the continuation of therapeutic anticoagulation, such as a high-risk thrombophilia. Prophylactic anticoagulation should be continued for up to 6 weeks postpartum.

Though the risk of HIT is lower with LMWH, the authors still monitor platelet counts by checking a complete blood cell count on day 3, once between days 7 through 10, and then monthly after starting anticoagulation. Finally, the authors typically convert patients to unfractionated heparin at 36 weeks in anticipation of labor and possible regional anesthesia as regional anesthesia is contraindicated within 18 to 24 hours of therapeutic LMWH administration. Patients should be advised to hold their anticoagulation at the onset of labor. Heparin should be discontinued 24 hours before induction of labor or planned cesarean section. If spontaneous labor occurs in women receiving unfractionated heparin, careful monitoring of the aPTT is required [20].

In the postpartum period, prophylactic anticoagulation should be restarted 3 to 6 hours after vaginal delivery and 6 to 8 hours after uncomplicated cesarean delivery. The authors either continue enoxaparin (40 mg daily) or transition to oral anticoagulant therapy with warfarin. Warfarin should be dosed to achieve an international normalized ratio of 2.0 to 3.0 and enoxaparin must be continued for 5 days and until the international normalized ratio is therapeutic for 2 days. Because of the need with warfarin therapy for frequent monitoring of the international normalized ratio, most patients prefer to simply continue the enoxaparin.

Summary

Venous thromboembolism is one of the most critical clinical emergencies an obstetrician/gynecologist will confront. An understanding of the physiology and pathophysiology of hemostasis and thrombosis in pregnancy is essential and allows the clinician to predict which patients are at highest risk. Prompt recognition and diagnosis of venous thromboembolism with contemporary imaging modalities allow for the timely initiation of appropriate therapy to prevent further maternal and fetal morbidity.

References

[1] Chang J, Elam-Evans L, Berg C, et al. Pregnancy-related mortality surveillance—United States, 1991–1999. MMWR Surveill Summ 2003;52:1–8.
[2] Greer I. Thrombosis in pregnancy: maternal and fetal issues. Lancet 1999;353(9160): 1258–65.
[3] Gherman RB, Goodwin TM, Leung B, et al. Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy. Obstet Gynecol 1999;94(5 Pt 1):730–4.
[4] Ginsberg J, Brill-Edwards P, Burrows R, et al. Venous thrombosis during pregnancy: leg and trimester of presentation. Thromb Haemost 1992;67:519–20.
[5] James K, Lohr J, Deshmukh R, et al. Venous thrombotic complications of pregnancy. Cardiovasc Surg 1996;4:777–82.
[6] Kierkegaard A. Incidence and diagnosis of deep vein thrombosis associated with pregnancy. Acta Obstet Gynecol Scand 1983;62:239–43.
[7] Martin S, Foley M. Intensive care in obstetrics: an evidence-based review. Am J Obstet Gynecol 2006;195(3):673–89.

[8] Rutherford S, Montoro M, McGehee W, et al. Thromboembolic disease associated with pregnancy: an 11-year review (SPO Abstract). Obstet Gynecol 1991;164:286.

[9] Simpson E, Lawrenson R, Nightingale A, et al. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. BJOG 2001;108:56–60.

[10] Stein P, Hull R, Patel K, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. Ann Intern Med 2004;140:589–602.

[11] Blanco-Molina A, Trujillo-Santos J, Criado J, et al. Venous thromboembolism during pregnancy or postpartum: findings from the RIETE registry. Thromb Haemost 2007; 97(2):186–90.

[12] McColl M, Ramsay J, Tait R, et al. Risk factors for pregnancy associated venous thromboembolism. Thromb Haemost 1997;78:1183–8.

[13] Macklon N, Greer I. Venous thromboembolic disease in obstetrics and gynecology: the Scottish experience. Scott Med J 1996;41:83–6.

[14] Lindqvist P, Dahlback B, Marsal K. Thrombotic risk during pregnancy: a population study. Obstet Gynecol 1999;94(4):595–9.

[15] Tengborn L, Bergqvist D, Matzsch T, et al. Recurrent thromboembolism in pregnancy and puerperium. Is there a need for thromboprophylaxis? Am J Obstet Gynecol 1989;160(1):90–4.

[16] Brill-Edwards P, Ginsberg JS, Gent M, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. N Engl J Med 2000;343(20):1439–44.

[17] De Stefano V, Martinelli I, Rossi E, et al. The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. Br J Haematol 2006; 135(3):386–91.

[18] Barbour LA, Smith JM, Marlar RA. Heparin levels to guide thromboembolism prophylaxis during pregnancy. Am J Obstet Gynecol 1995;173(6):1869–73.

[19] Quiñones J, James D, Stamilio D, et al. Thromboprophylaxis after cesarean delivery: a decision analysis. Obstet Gynecol 2005;106(4):733–40.

[20] Bates S, Greer I, Hirsh J, et al. Use of antithrombotic agents during pregnancy: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126:627S–44S.

[21] Krivak T, Zorn K. Venous thromboembolism in obstetrics and gynecology. Obstet Gynecol 2007;109(3):761–77.

[22] Gerhardt A, Scharf R, Beckmann M, et al. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. N Engl J Med 2000;342: 374–80.

[23] Grandone E, Margaglione M, Colaizzo D, et al. Genetic susceptibility to pregnancy-related venous thromboembolism: roles of factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T mutations. Am J Obstet Gynecol 1998;179(5):1324–8.

[24] Ruggeri Z, Dent J, Saldivar E. Contribution of distinct adhesive interactions to platelet aggregation in flowing blood. Blood 1999;94:172–8.

[25] Pytela R, Pierschbacher M, Ginsberg M, et al. Platelet membrane glycoprotein IIb/IIIa: member of a family of Arg-Gly-Asp-specific adhesion receptors. Science 1986;231:1559–62.

[26] Nemerson Y. Tissue factor and hemostasis. Blood 1988;71:1–8.

[27] Preissner K, de Boer H, Pannekoek H, et al. Thrombin regulation by physiological inhibitors: the role of vitronectin. Semin Thromb Hemost 1996;165:1335–41.

[28] Broze G. The rediscovery and isolation of TFPI. J Thromb Haemost 2003;1:1671–5.

[29] Schatz F, Lockwood C. Progestin regulation of plasminogen activator inhibitor type-1 in primary cultures of endometrial stromal and decidual cells. J Clin Endocrinol Metab 1993;77:621–5.

[30] Lockwood C, Krikun G, Schatz F. The decidua regulates hemostasis in the human endometrium. Semin Reprod Endocrinol 1999;17:45–51.

[31] Bremme K. Haemostatic changes in pregnancy. Baillieres Best Pract Res Clin Haematol 2003;16:153–68.

[32] Hellgren M, Blomback M. Studies on blood coagulation and fibrinolysis in pregnancy, during delivery and in the puerperium. Gynecol Obstet Invest 1981;12:141–54.

[33] Ginsberg J, Wells P, Brill-Edwards P, et al. Antiphospholipid antibodies and venous thromboembolism. Blood 1995;86(10):3685–91.

[34] Girling J, de Swiet M. Inherited thrombophilia and pregnancy. Curr Opin Obstet Gynecol 1998;10:135–44.

[35] Garcia-Fuster M, Fernandez C, Forner M, et al. Risk factors and clinical characteristics of thromboembolic venous disease in young patients: a prospective study. Med Clin (Barc) 2004;123:217–9.

[36] Branch D, Silver R, Blackwell J, et al. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynecol 1992;80: 612–20.

[37] Wessler S. Medical management of venous thrombosis. Annu Rev Med 1976;27:313–9.

[38] Hirsh J, Hoak J. Management of deep vein thrombosis and pulmonary embolism: a statement for healthcare professionals from the council on thrombosis (in consultation with the council on cardiovascular radiology), American Heart Association. Circulation 1996;93: 2212–45.

[39] Sandler D, Martin J, Duncan J, et al. Diagnosis of deep-vein thrombosis: comparison of clinical evaluation, ultrasound, plethysmography, and venoscan with X-ray venogram. Lancet 1984;8405:716–9.

[40] Stein PD, Hull RD, Pineo G. Strategy that includes serial noninvasive leg tests for diagnosis of thromboembolic disease in patients with suspected acute pulmonary embolism based on data from PIOPED. Prospective investigation of pulmonary embolism diagnosis. Arch Intern Med 1995;155(19):2101–4.

[41] Douketis JD, Ginsberg JS. Diagnostic problems with venous thromboembolic disease in pregnancy. Haemostasis 1995;25(1–2):58–71.

[42] Eichinger S. D-dimer testing in pregnancy. Pathophysiol Haemost Thromb 2003;33(5–6): 327–9.

[43] Kelly J, Hunt BJ. A clinical probability assessment and D-dimer measurement should be the initial step in the investigation of suspected venous thromboembolism. Chest 2003; 124(3):1116–9.

[44] Wells PS, Anderson DR, Ginsberg J. Assessment of deep vein thrombosis or pulmonary embolism by the combined use of clinical model and noninvasive diagnostic tests. Semin Thromb Hemost 2000;26(6):643–56.

[45] Ghirardini G, Battioni M, Bertellini C, et al. D-dimer after delivery in uncomplicated pregnancies. Clin Exp Obstet Gynecol 1999;26(3–4):211–2.

[46] Francalanci I, Comeglio P, Liotta A, et al. D-dimer concentrations during normal pregnancy, as measured by ELISA. Thromb Res 1995;78(5):399–405.

[47] Ballegeer V, Mombaerts P, Declerck PJ, et al. Fibrinolytic response to venous occlusion and fibrin fragment D-dimer levels in normal and complicated pregnancy. Thromb Haemost 1987;58(4):1030–2.

[48] Nolan TE, Smith RP, Devoe LD. Maternal plasma D-dimer levels in normal and complicated pregnancies. Obstet Gynecol 1993;81(2):235–8.

[49] Bounameaux H, de Moerloose P, Perrrier A, et al. Plasma measurement of D-dimer as a diagnostic aid in suspected venous thromboembolism: an overview. Thromb Haemost 1994; 71:1–6.

[50] Heim S, Schectman J, Siadaty M, et al. D-dimer testing for deep venous thrombosis: a meta-analysis. Clin Chem 2004;50(7):1136–47.

[51] Wells P, Anderson D, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003;349:1227–35.

[52] Wells P, Hirsh J, Anderson D, et al. A simple clinical model for the diagnosis of deep-vein thrombosis combined with impedance plethysmography: potential for an improvement in the diagnostic process. J Intern Med 1998;243:15–23.

[53] British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax 2003;58(6):470–83.

[54] Polak JF, Wilkinson DL. Ultrasonographic diagnosis of symptomatic deep venous thrombosis in pregnancy. Am J Obstet Gynecol 1991;165(3):625–9.

[55] Kassai B, Boissel J, Cucherat M, et al. A systematic review of the accuracy of ultrasound in the diagnosis of deep venous thrombosis in asymptomatic patients. Thromb Haemost 2004; 91:655–66.

[56] Gottlieb R, Widjaja J, Tian L, et al. Calf sonography for detecting deep venous thrombosis in symptomatic patients: experience and review of the literature. J Clin Ultrasound 1999;27:415–20.

[57] Palareti G, Cosmi B, Legnani C. Diagnosis of deep vein thrombosis. Semin Thromb Hemost 2006;32(7):659–72.

[58] Moody AR. Magnetic resonance direct thrombus imaging. J Thromb Haemost 2003;1(7): 1403–9.

[59] Fraser DG, Moody AR, Morgan PS, et al. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. Ann Intern Med 2002;136(2):89–98.

[60] Carpenter J, Holland G, Baum R, et al. Magnetic resonance venography for the detection of deep venous thrombosis: comparison with contrast venography and duplex Doppler ultrasonography. J Vasc Surg 1993;18:734–41.

[61] Spritzer CE, Evans AC, Kay HH. Magnetic resonance imaging of deep venous thrombosis in pregnant women with lower extremity edema. Obstet Gynecol 1995;85(4):603–7.

[62] Kanal E, Shellock FG. Policies, guidelines, and recommendations for MR imaging safety and patient management. SMRI Safety Committee. J Magn Reson Imaging 1992;2(2): 247–8.

[63] Loud PA, Katz DS, Klippenstein DL, et al. Combined CT venography and pulmonary angiography in suspected thromboembolic disease: diagnostic accuracy for deep venous evaluation. AJR Am J Roentgenol 2000;174(1):61–5.

[64] Garg K, Kemp JL, Wojcik D, et al. Thromboembolic disease: comparison of combined CT pulmonary angiography and venography with bilateral leg sonography in 70 patients. AJR Am J Roentgenol 2000;175(4):997–1001.

[65] Duwe KM, Shiau M, Budorick NE, et al. Evaluation of the lower extremity veins in patients with suspected pulmonary embolism: a retrospective comparison of helical CT venography and sonography. 2000 ARRS Executive Council Award I. American Roentgen Ray Society. AJR Am J Roentgenol 2000;175(6):1525–31.

[66] Heijboer H, Cogo A, Buller H, et al. Detection of deep vein thrombosis with impedance plethysmography and real-time compression ultrasonography in hospitalized patients. Arch Intern Med 1992;152:1901–3.

[67] Matthews S. Short communication: imaging pulmonary embolism in pregnancy: what is the most appropriate imaging protocol? Br J Radiol 2006;79(941):441–4.

[68] Chan W, Ray J, Murray S, et al. Suspected pulmonary embolism in pregnancy: clinical presentation, results of lung scanning, and subsequent maternal and pediatric outcomes. Arch Intern Med 2002;162(10):1170–5.

[69] Fedullo P, Tapson V. The evaluation of suspected pulmonary embolism. N Engl J Med 2003;349:1247–56.

[70] Stein P, Terrin M, Hales C, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest 1991;100:598–603.

[71] Green R, Meyer T, Dunn M, et al. Pulmonary embolism in younger adults. Chest 1992;101: 1507–11.

[72] Powrie RO, Larson L, Rosene-Montella K, et al. Alveolar-arterial oxygen gradient in acute pulmonary embolism in pregnancy. Am J Obstet Gynecol 1998;178(2):394–6.

[73] The urokinase pulmonary embolism trial: a national cooperative study. Circulation 1973; 47(Suppl II):1–108.

[74] Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the pro-spective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED investi-gators. JAMA 1990;263:2653–9.

[75] Rodger M, Makropoulos D, Turek M, et al. Diagnostic value of the electrocardiogram in suspected pulmonary embolism. Am J Cardiol 2000;86:807–9.

[76] Tapson V, Carroll B, Davidson B, et al. The diagnostic approach to acute venous throm-boembolism. Clinical practice guideline. American Thoracic Society. Am J Respir Crit Care Med 1999;160:1043–66.

[77] Come P. Echocardiographic evaluation of pulmonary embolism and its response to thera-peutic interventions. Chest 1992;101:151S–62S.

[78] Gibson N, Sohne M, Buller H. Prognostic value of echocardiography and spiral com-puted tomography in patients with pulmonary embolism. Curr Opin Pulm Med 2005; 11:380–4.

[79] Pruszczyk P, Torbicki A, Pacho R, et al. Noninvasive diagnosis of suspected severe pulmo-nary embolism: transesophageal echocardiography vs spiral CT. Chest 1997;112:722–8.

[80] Giannitsis E, Muller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation 2000;102(2):211–7.

[81] Meyer T, Binder L, Hruska N, et al. Cardiac troponin I elevation in acute pulmonary em-bolism is associated with right ventricular dysfunction. J Am Coll Cardiol 2000;36(5): 1632–6.

[82] Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002;106(10): 1263–8.

[83] Douketis JD, Leeuwenkamp O, Grobara P, et al. The incidence and prognostic significance of elevated cardiac troponins in patients with submassive pulmonary embolism. J Thromb Haemost 2005;3(3):508–13.

[84] Dalen J, Brooks H, Johnson L, et al. Pulmonary angiography in acute pulmonary embo-lism: indications, techniques, and results in 367 patients. Am Heart J 1971;81:175–85.

[85] Mills S, Jackson D, Older R, et al. The incidence, etiologies, and avoidance of complications of pulmonary angiography in a large series. Radiology 1980;136:295–9.

[86] Stein P, Athanasoulis C, Alavi A, et al. Complications and validity of pulmonary angiog-raphy in acute pulmonary embolism. Circulation 1992;85:462–8.

[87] Balan KK, Critchley M, Vedavathy KK, et al. The value of ventilation-perfusion imaging in pregnancy. Br J Radiol 1997;70(832):338–40.

[88] Winer-Muram H, Boone J, Brown H, et al. Pulmonary embolism in pregnant patients: fetal radiation dose with helical CT. Radiology 2002;224(2):487–92.

[89] Groves A, Yates S, Win T, et al. CT pulmonary angiography versus ventilation-perfusion scintigraphy in pregnancy: implications from a UK survey of doctors' knowledge of radi-ation exposure. Radiology 2006;240(3):765–70.

[90] Stein P, Woodard P, Weg J, et al. Diagnostic pathways in acute pulmonary embolism: rec-ommendations of the PIOPED II Investigators. Radiology 2007;242(1):15–21.

[91] Schuster M, Fishman J, Copeland J, et al. Pulmonary embolism in pregnant patients: a sur-vey of practices and policies for CT pulmonary angiography. AJR Am J Roentgenol 2003; 181(6):1495–8.

[92] Quiroz R, Kucher N, Zou K, et al. Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: a systematic review. JAMA 2005; 293(16):2012–7.

[93] Moores LK, Jackson WL Jr, Shorr AF, et al. Meta-analysis: outcomes in patients with sus-pected pulmonary embolism managed with computed tomographic pulmonary angiogra-phy. Ann Intern Med 2004;141(11):866–74.

[94] Hayashino Y, Goto M, Noguchi Y, et al. Ventilation-perfusion scanning and helical CT in suspected pulmonary embolism: meta-analysis of diagnostic performance. Radiology 2005; 234(3):740–8.

[95] Doyle NM, Ramirez MM, Mastrobattista JM, et al. Diagnosis of pulmonary embolism: a cost-effectiveness analysis. Am J Obstet Gynecol 2004;191(3):1019–23.

[96] Meaney J, Weg J, Chenevert T, et al. Diagnosis of pulmonary embolism with magnetic resonance angiography. N Engl J Med 1997;336:1422–7.

[97] Oudkerk M, van Beek EJ, Wielopolski P, et al. Comparison of contrast-enhanced magnetic resonance angiography and conventional pulmonary angiography for the diagnosis of pulmonary embolism: a prospective study. Lancet 2002;359(9318):1643–7.

[98] Kluge A, Mueller C, Strunk J, et al. Experience in 207 combined MRI examinations for acute pulmonary embolism and deep vein thrombosis. AJR Am J Roentgenol 2006; 186(6):1686–96.

[99] Hirsh J. Heparin. N Engl J Med 1991;324:1565–74.

[100] Raschke R, Reilly B, Guidry J, et al. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. Ann Intern Med 1993;119:874–81.

[101] Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol 1993;168(4):1265–70.

[102] Warkentin T, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:311S–37S.

[103] Gould M, Dembitzer A, Doyle R, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. Ann Intern Med 1999;130(10):800–9.

[104] Jacobsen A, Qvigstad E, Sandset P. Low molecular weight heparin (dalteparin) for the treatment of venous thromboembolism in pregnancy. BJOG 2003;110(2):139–44.

[105] Lepercq J, Conard J, Borel-Derlon A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. BJOG 2001;108:1134–40.

[106] Sanson B, Lensing A, Prins M, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. Thromb Haemost 1999;81(5):668–72.

[107] Ginsberg J, Hirsh J, Turner D, et al. Risks to the fetus of anticoagulant therapy during pregnancy. Thromb Haemost 1989;61:197–203.

[108] Shefras J, Farquharson RG. Bone density studies in pregnant women receiving heparin. Eur J Obstet Gynecol Reprod Biol 1996;65(2):171–4.

[109] Pettila V, Leinonen P, Markkola A, et al. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. Thromb Haemost 2002;87(2):182–6.

[110] Rodie V, Thomson A, Stewart F, et al. Low molecular weight heparin for the treatment of venous thromboembolism in pregnancy: a case series. BJOG 2002;109(9):1020–4.

[111] McColl M, Greer I. Low-molecular-weight heparin for the prevention and treatment of venous thromboembolism in pregnancy. Curr Opin Pulm Med 2004;10(5):371–5.

[112] Gould M, Dembitzer A, Sanders G, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. Ann Intern Med 1999;130(10):789–99.

[113] Barbour L, Oja J, Schultz L. A prospective trial that demonstrates that dalteparin requirements increase in pregnancy to maintain therapeutic levels of anticoagulation. Am J Obstet Gynecol 2004;191:1024–9.

[114] Wells PS, Kovacs MJ, Bormanis J, et al. Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin: a comparison of patient self-injection with homecare injection. Arch Intern Med 1998; 158(16):1809–12.