Deep vein thrombosis in pregnancy: Epidemiology, pathogenesis, and diagnosis

Authors: Atul Malhotra, MD, Steven E Weinberger, MD
Section Editors: Lawrence LK Leung, MD, Charles J Lockwood, MD, MHCM, Jess Mandel, MD
Deputy Editor: Geraldine Finlay, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2019. | **This topic last updated:** Nov 01, 2018.

INTRODUCTION

Pregnancy and the puerperium (postpartum period) are well-established risk factors for venous thromboembolism (VTE), which occurs with a prevalence of 1 in 1600 [1-7]. The overlap with symptoms of pregnancy may impair clinical suspicion making diagnosis of VTE more challenging.

VTE can manifest during pregnancy as an isolated lower extremity deep vein thrombosis (DVT) or clot can break off from the lower extremities and travel to the lung to present as a pulmonary embolus (PE) [8-10]. PE is the seventh leading cause of maternal mortality, responsible for 9 percent of maternal deaths [11-13]. Thus, the detection of DVT during pregnancy is critical to preventing deaths from PE.

The epidemiology, pathogenesis, and diagnosis of DVT during pregnancy and the puerperium will be reviewed here. The epidemiology, pathogenesis, and diagnosis of PE, as well as the prevention and treatment of DVT and PE during pregnancy are discussed separately. (See "Pulmonary embolism in pregnancy: Epidemiology, pathogenesis, and diagnosis" and "Deep vein thrombosis and pulmonary embolism in pregnancy: Prevention" and "Deep vein thrombosis and pulmonary embolism in pregnancy: Treatment" and "Use of anticoagulants during pregnancy and postpartum".)

EPIDEMIOLOGY

The overall prevalence of venous thromboembolism (VTE) in pregnancy is low. In the United States, VTE is diagnosed during 1 in 500 to 2000 pregnancies (absolute incidence; 0.025 to 0.1 percent) [1-6,14]. In a retrospective case-control study of 395,335 pregnant women at 24 weeks of

gestation, the incidence of VTE was 85 per 100,000 pregnancies [15]. A population-based inception cohort study over a 30 year period detected an overall incidence of VTE of 200 per 100,000 woman-years [5]. DVT was three times more common than PE [5].

Similar rates are observed in Europe [2,5]. In one retrospective study of over 72,000 deliveries, the incidence of DVT was 0.71 per 1000 deliveries (95% CI 0.5-0.9) with 0.5 (95% CI 0.34-0.66) and 0.21 (95% CI 0.11-0.31) occurring antenatally and postnatally, respectively [16]. The incidence of PE was 0.15 per 1000 deliveries (95% CI 0.06-0.24) with 0.07 (95% CI 0.01-0.13) and 0.08 (95% CI 0.02-0.14) occurring antenatally and postnatally, respectively [16].

PE is the seventh leading cause of maternal mortality and accounts for 9 percent of maternal deaths [17-19].

Pregnancy-related mortality has the largest racial disparity among the maternal and child health indicators [11,20]. Black women have a three to four times higher pregnancy related mortality ratio than white women. Although the reasons for this cannot be directly attributed to increased rates of VTE, compared to white women, deaths from VTE are higher in black women [11]. Additionally, compared to white or Asian women, black women had a higher risk of VTE (odds ratio 1.5) [20].

Two studies suggest that the incidence of VTE appears to be decreasing over the last three decades, largely due to a decrease in the incidence of VTE in the postpartum period [5,21]. The reasons for this change are unclear but could be explained by a general increase in the use of thromboprophylaxis in the postpartum period. In contrast, another study reports a 14 percent increase in VTE-associated pregnancy hospitalizations between 1994 and 2009, with a concomitant increase in comorbid conditions such as obesity and hypertension among those admitted for VTE [22].

RISK FACTORS

Pregnancy, in itself, is a risk factor for the development of venous thromboembolism (VTE) with a reported incidence that is 4 to 50 times higher compared to nonpregnant women [1-7]. Increased risk for VTE is highest in the postpartum period, with a higher than usual prevalence of clot in the left lower extremity and pelvis. In addition, risk is augmented further in women with inherited thrombophilias. These risk factors are discussed in the following sections.

A risk model for VTE within the first six weeks postpartum has been developed and externally validated, based upon two large European cohorts [14]. Among the many factors that contribute to the model, those associated with the highest risk were emergency cesarean section, stillbirth, varicose veins, pre-eclampsia/eclampsia, postpartum infection, and comorbidities. Further validation is needed to confirm these results.

Timing during pregnancy — Compared to the nonpregnant population, the risk of VTE is higher in all stages of pregnancy. However, it is greatest in the postpartum period. The identified risk factors associated with the antepartum and postpartum periods are listed below.

- **Antepartum** – Most studies report equal distribution of VTE across the trimesters of pregnancy [1,2,15,21,23-26]. However, two large conflicting retrospective studies reported a first trimester predominance (50 percent before 15 weeks) and third trimester predominance (60 percent), respectively [27,28]. Factors that increase the risk of VTE antepartum are less well described but include the following:
  - Multiple births [15]
  - Varicose veins [29]
  - Inflammatory bowel disease [29]
  - Urinary tract infection [29]
  - Diabetes [29]
  - Hospitalization for non-delivery reasons (particularly those >3 days) [30]
  - Body mass index (BMI) ≥30 kg/m^2 [30]
  - Increased maternal age ≥35 years [30]
- **Postpartum** – Compared with the antepartum period, VTE is two to five times more common postpartum [5,15,21,23,24,26,28,31-33]. The risk is highest in the first six weeks postpartum and declines to rates that approximate that of the general population by about 13 to 18 weeks [31].

  Commonly cited factors that increase the risk of VTE postpartum include the following:
  - Cesarean section (CS), especially emergent CS [21,29,31-34]
  - Medical comorbidities (eg, varicose veins, cardiac disease, inflammatory bowel disease) [15,29]
  - BMI ≥25 kg/m^2 [15,29,33]
  - Young gestational age (preterm delivery <36 weeks) [15,26,28,29,33]
  - Obstetric hemorrhage [29,32,33]
  - Stillbirth [29]
  - Increased maternal age ≥35 years [15,31]

- Hypertension [21]
- Smoking [31,35]
- Eclampsia or preeclampsia [31-33]
- Postpartum infection [32,33]

Thrombotic risk is highest in the first six weeks postpartum and although the risk persists until 12 weeks, the absolute risk beyond six weeks appears to be low. Data best illustrating this persistent (though attenuated) postpartum thrombotic risk are derived from a five year retrospective crossover-cohort analysis of an insurance claims database including almost 1.7 million women that examined rates of thrombosis during the first year following delivery [31]. VTE accounted for the majority (68 percent) of reported thrombotic events followed by stroke (28 percent) and myocardial infarction (4 percent). Compared to rates at one year, the risk of thrombosis was highest in the first six weeks postpartum (25 versus 2 per 100,000 deliveries; odds ratio [OR] 11, 95% CI 8-15) and declined to lower but still elevated rates at 7 to 12 weeks (6 versus 3 per 100,000 deliveries; OR 2, 95% CI 1.5-3.1). Rates were close to that of the general population by 13 to 18 weeks (3 versus 2 per 100,000 deliveries; OR 1.4, 95% CI 0.9-2.1). As compared with patients without postpartum thrombosis, those with thrombotic events were more likely to be older (≥35 years), have risk factors for thrombosis (eg, eclampsia, hypercoagulable state, smoking, cesarean section) and be white or black rather than Hispanic or Asian.

Anatomic location of deep vein thrombosis (DVT) — The majority of lower extremity DVTs during pregnancy are left-sided. In addition, the incidence of pelvic vein thrombosis is significantly higher during pregnancy and the puerperium, although DVT remains most often found in the proximal veins (eg, femoral vein). No studies describe an increased incidence of upper extremity DVT during pregnancy or the puerperium.

- **Left lower extremity DVT** – DVT is predominantly left-sided in pregnancy (70 to 90 percent). In one study of 60 pregnant women with a first episode of VTE, there were 58 isolated left lower extremity DVTs, two bilateral DVTs, and no isolated right lower extremity DVTs [23]. In another retrospective study, of 124 pregnant women with a diagnosis of DVT, involvement of the left leg was reported in 88 percent of the 96 patients for whom the affected side was known [36]. This striking distribution has been attributed to increased venous stasis in the left leg related to compression of the left iliac vein by the right iliac artery, coupled with compression of the inferior vena cava by the gravid uterus [23,37,38]. (See "Overview of the causes of venous thrombosis", section on 'May-Thurner syndrome'.)

- **Pelvic vein DVT** – Pelvic vein DVT is more commonly diagnosed in pregnancy than in the general population. However, its true prevalence during pregnancy is unknown. This may be due to the poor sensitivity of compressive proximal vein ultrasound for the diagnosis of

thrombosis in the pelvic veins [39]. In an analysis of the DVT-Free Registry enrolling 5451 consecutive patients with ultrasound-confirmed DVT, the rates of isolated pelvic vein DVT were higher antepartum and postpartum women than those in nonpregnant women (12 percent and 11 percent versus 1 percent, respectively) [7]. Another retrospective study of 124 pregnant women showed 64 percent of proximal DVTs were restricted to the iliac and/or femoral vein [36].

Inherited thrombophilias — The risk of VTE is further magnified in pregnant women who have inherited thrombophilias [4,16,40-45]. The inherited thrombophilias during pregnancy are discussed in detail separately. (See "Inherited thrombophilias in pregnancy".)

In brief, the variable range in risk of VTE in pregnant patients with the most common inherited thrombophilias is illustrated by the following studies:

- Compared to the general population, the thrombotic risk is three times higher for pregnant women with factor V Leiden [16]. Further augmenting that risk in pregnant patients with factor V Leiden deficiency and G20210A prothrombin-gene mutation is a history of prior VTE in the patient or an affected first-degree relative (up to 50-fold) [45]. (See "Factor V Leiden and activated protein C resistance" and "Prothrombin G20210A mutation", section on 'Obstetric issues'.)

- When compared with pregnant women without a known thrombophilia, pregnant women with an inheritable deficiency of antithrombin III, protein S, or protein C had an eight-fold increased risk of venous thrombosis in the antepartum and postpartum periods combined [40]. (See "Antithrombin deficiency" and "Protein S deficiency" and "Protein C deficiency".)

- Among women with known antiphospholipid syndrome, one prospective study described a 5 percent risk of thrombosis during pregnancy [46]. (See "Clinical manifestations of antiphospholipid syndrome".)

PATHOGENESIS

Pregnancy and the postpartum period are marked by the presence of all three components of Virchow's triad: venous stasis, endothelial injury, and a hypercoagulable state [2]. All features likely contribute to the increased risk of venous thromboembolism (VTE) in pregnancy.

Stasis — Venous stasis of the lower extremities occurs during pregnancy because of two factors: pregnancy-associated changes in venous capacitance and compression of large veins by the gravid uterus. The lower extremity veins of pregnant patients appear to be subject to increased stasis even before the uterus has enlarged substantially. Although blood volume and total venous return are supranormal in pregnancy, the linear flow velocity in the lower extremity veins is decreased due to hormonally induced dilation of capacitance veins, leading to venous pooling and

valvular incompetence [47]. (See "Maternal adaptations to pregnancy: Cardiovascular and hemodynamic changes".)

These early changes are amplified by inferior vena caval and iliac vein compression by the gravid uterus [47,48]. One study that assessed 24 pregnant women with monthly compressive ultrasound examinations found progressive dilation of the deep veins of the legs during gestation [49]. This corresponded to a decreased flow velocity in the left common femoral vein and inferior vena cava that was most severe in the supine position. Assuming the left lateral decubitus position significantly increased the velocity in both lower extremities. In addition, as noted above, compression of the left iliac vein by the right iliac artery is thought to contribute to the predilection of left-sided deep vein thrombosis (DVT) during pregnancy [1,8].

Endothelial injury — Delivery is associated with vascular injury and changes at the uteroplacental surface, which probably contribute to the increased risk of VTE in the immediate postpartum period. Forceps, vacuum extraction, or surgical delivery can exaggerate vascular intimal injury and amplify this phenomenon [1].

Hypercoagulability — Pregnancy is a hypercoagulable state associated with progressive increases in several coagulation factors, including factors I, II, VII, VIII, IX, and X, along with a decrease in protein S [1,16,50]. A progressive increase in resistance to activated protein C is normally observed in the second and third trimesters [51], and high resistance to activated protein C was shown in one study to be associated with an increased risk for pregnancy-related venous thrombosis [52]. Activity of the fibrinolytic inhibitors PAI-1 and PAI-2 is increased during pregnancy, although total fibrinolytic activity may not be impaired [53,54].

CLINICAL PRESENTATION

The clinical features of deep vein thrombosis (DVT) in pregnancy and the puerperium overlap with many of the features of normal pregnancy. Thus, distinguishing the features associated with the hemodynamic changes of pregnancy from clinically important DVT can be difficult. (See "Clinical manifestations and diagnosis of early pregnancy", section on 'Clinical manifestations of early pregnancy' and "Maternal adaptations to pregnancy: Cardiovascular and hemodynamic changes".)

Other than the higher propensity to develop left-sided DVT and iliac vein thrombosis, the clinical presentation of DVT during pregnancy is identical to that in nonpregnant women.

Signs and symptoms suggestive of proximal vein thrombosis are diffuse pain and swelling that may or may not be associated with erythema, warmth and tenderness of the lower extremity. Symptoms of iliac vein thrombosis include swelling of the entire leg with or without flank, lower abdomen, buttock, or back pain [55,56]. The clinical signs and symptoms of DVT in nonpregnant patients are discussed separately. (See "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity".)

LABORATORY TESTING

Compared to its value in the general population, D-dimer has limited diagnostic value in pregnant women suspected of having a deep vein thrombosis (DVT). Arterial blood gases are not indicated routinely in the diagnosis of DVT. Laboratory testing for suspected DVT in the nonpregnant patient is discussed separately. (See "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity".)

D-dimer — Assays (enzyme-linked, turbidimetric, hemagglutination) for serum D-dimer, a breakdown product of cross-linked fibrin, have been extensively studied for use in the diagnosis of DVT. In nonpregnant patients, the negative predictive value of D-dimer in ruling out DVT is high, particularly when combined with clinical probability models or with a negative compressive ultrasound. However, in pregnancy, although the negative predictive value remains high, the test is not as useful due to increased levels of D-dimer during pregnancy. The assays used and the diagnostic utility of D-dimer in nonpregnant patients are discussed in detail separately. (See "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity", section on 'D-dimer'.)

The limited utility of D-dimer in pregnancy is largely due to the natural rise in D-dimer with each trimester and slow decline postpartum. The natural course of D-dimer levels has not been well studied so there are no established normal reference ranges for the antepartum and postpartum periods. Thus, altered levels of D-dimer throughout pregnancy and the puerperium are subject to misinterpretation.

The following studies have confirmed the limited value of D-dimer during pregnancy:

- In a study of 50 pregnant women without venous thrombosis, D-dimer levels increased with each trimester such that 22 percent of women in the second trimester and none in the third trimester had a normal D-dimer concentration (ie, <500 ng/mL) [57].
- In another study of 149 consecutive pregnant women presenting with suspected DVT, in whom this diagnosis was ruled out by compression ultrasonography, D-dimer was negative in 100, 76, and 49 percent of those in the first, second, and third trimester, respectively [58].
- Two small studies confirmed that pregnant women with DVT had higher D-dimer levels than pregnant women without DVT [59,60]. Using higher cut-off values resulted in maintenance of high sensitivity (80 to 100 percent) and improved specificity (62 to 79 percent) of D-dimer for DVT diagnosis ("moderate to high sensitivity" D-dimer) [59]. Validation in prospective studies is needed before higher cut-off values of D-dimer are used as a routine pretest probability tool during pregnancy.

IMAGING

Much of the data to support imaging studies for the diagnosis of DVT in pregnancy is extrapolated from large studies in the nonpregnant population with smaller studies suggesting similar efficacy in pregnancy. The diagnosis of DVT during pregnancy is most often made by demonstrating poor compressibility of the proximal veins on compressive ultrasonography (CUS). The diagnosis is rarely made by the demonstration of a filling defect on contrast or magnetic resonance venography.

Proximal vein CUS is a highly sensitive and specific tool for the diagnosis of DVT in both pregnant and nonpregnant patients. However, it is less sensitive for pelvic vein thrombosis (more common in pregnancy) and for calf vein thrombosis (less common in pregnancy) [39]. In cases where CUS is negative, poor Doppler flow in the iliac vein has reasonable accuracy for the diagnosis of suspected pelvic vein DVT; serial compressive ultrasound is a sensitive strategy that can be used to follow suspected calf vein DVT in the rare circumstance that it propagates proximally. The approach to diagnosing suspected DVT in pregnancy is discussed in detail separately. (See 'Diagnostic algorithm' below.)

Compression ultrasonography — In pregnant patients, poor compressibility of a thigh vein with the ultrasound probe is highly sensitive (95 percent) and specific (>95 percent) for the diagnosis of symptomatic proximal vein thrombosis [61]. The addition of Doppler analysis of flow variation with respiration with the patient in the left lateral decubitus position assists in diagnosing isolated iliac vein thrombosis during pregnancy [49]. When positive, the diagnosis of DVT by CUS in a pregnant patient should prompt immediate anticoagulation. (See "Deep vein thrombosis and pulmonary embolism in pregnancy: Treatment" and "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity", section on 'Diagnostic ultrasonography suspected first DVT'.)

CUS is less sensitive for pelvic vein thrombosis and for calf vein thrombosis [39]. In cases where CUS is negative, pelvic vein thrombosis may be suspected when the visualized vein is compressible but there is absence of normal changes in flow during respiration or with the Valsalva maneuver. Serial CUS can be used to detect suspected calf vein thrombosis that propagates proximally as the pregnancy progresses.

Serial compression ultrasonography — Proximal vein CUS is less sensitive for the diagnosis of calf vein thrombosis than for proximal vein thrombosis [39]. In nonpregnant patients, calf vein thromboses can propagate proximally in approximately 20 percent of cases [62]. Serial CUS (performed on days 3 and 7) has been well validated in nonpregnant patients with suspected DVT for the detection of calf DVT in the setting of an initially negative ultrasound [62-64]. Using this modality to follow nonpregnant patients with suspected DVT with initial negative CUS, only 2

percent are subsequently diagnosed with DVT [63,64]. A number of small prospective studies have replicated the same findings in pregnant patients.

- A multicenter, prospective study of 149 pregnant women with suspected DVT and negative initial CUS, in whom anticoagulation was withheld for three months, showed that serial proximal CUS (performed on day 3 and 7 post initial testing), had a false negative rate of 0.7 percent for the exclusion of DVT [58].

- A single center, prospective study of 221 women with suspected DVT and initial negative ultrasound showed that serial proximal CUS (days 3 and 7) excluded DVT with a sensitivity and negative predictive value of 94.1 and 99.5 percent, respectively, at three months [65].

- Two additional studies (one retrospective, one observational) in a similar population of pregnant patients imaged with serial whole leg CUS had very few DVTs detected in the followup period after initial negative testing [66,67].

These studies suggest that, similar to what is observed in the general population, serial CUS is valuable as a sensitive imaging modality to diagnose the rare case of calf DVT that propagates proximally during pregnancy. (See 'Diagnostic algorithm' below.)

Magnetic resonance venography — Magnetic resonance venography is a modality that can detect both thigh and pelvic vein DVT with a sensitivity that approaches 100 percent in the nonpregnant population [68]. Data are limited in pregnancy. However, small case series of pregnant patients suggested that this modality was useful for the diagnosis of pelvic and femoral vein thrombosis in situations where other noninvasive examinations were equivocal [69,70]. (See "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity", section on 'Alternative imaging'.)

Ascending contrast venography — Visualization of a filling defect by ascending contrast venography is considered the gold standard for the diagnosis of lower extremity DVT in the nonpregnant population [71,72]. Studies that measure the accuracy, sensitivity, and specificity of venography in pregnancy are lacking. Venography is rarely performed in pregnancy due to concerns regarding exposure of the fetus to ionizing radiation, technical difficulties of femoral vein cannulation, and decreased sensitivity for isolated iliofemoral thrombosis due to abdominal-pelvic shielding [1,56,61]. Additionally, the alternative imaging test, CUS, approaches venography in diagnostic sensitivity and specificity without these risks, rendering contrast venography less useful than in the past for the diagnosis of DVT [1,56,61]. (See "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity", section on 'Alternative imaging'.)

DIAGNOSTIC ALGORITHM

The successful diagnosis of suspected deep vein thrombosis (DVT) in pregnancy and the puerperium requires that clinicians have a high index of clinical suspicion and low threshold for use of objective confirmatory testing (algorithm 1). Our approach to the diagnosis of DVT during pregnancy is consistent with evidence-based practice guidelines published by the American College of Chest Physicians (ACCP) in 2012 and the American College of Obstetricians and Gynecologists in 2018 [73,74]. These guidelines are useful resources for the clinician to make decisions regarding testing and implementation of anticoagulation based upon the individual assessment of a pregnant patient with suspected DVT.

Pretest probability — Common predictive scoring systems (eg, Wells score), the LEFt clinical prediction rule, and D-dimer levels have all been described as potential clinical probability assessment tools for the diagnosis of suspected DVT. However, these tools have not been validated in large prospective trials and, in general, they are less useful in pregnant women than in the general population.

Wells score — The Wells and modified Wells scoring systems are the most commonly used scoring systems for nonpregnant patients with suspected DVT. However, they are not validated for use in pregnancy and should be interpreted with caution in this population. Of importance, some of the listed features (eg, active cancer, recent surgery) are not likely to be present in young healthy pregnant women while other features such as pitting edema and lower extremity tenderness are common symptoms of pregnancy in the absence of DVT. (See "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity".)

LEFt clinical prediction rule — The LEFt clinical prediction rule was developed on the rationale that DVT in pregnancy is predominantly left-sided [75,76]. A cross-sectional study evaluated clinical assessment in predicting the presence of a suspected first-time DVT in 194 pregnant women [75]. Three objective variables were highly predictive of DVT:

- Symptoms in the left leg (L for left)
- Calf circumference difference ≥2 cm (E for edema)
- First trimester presentation (Ft for first trimester presentation)

At least one of these variables was present in all 17 women (8.8 percent) with DVT. Among patients presenting with none, one, or two to three of these variables, DVT was diagnosed in zero, 16, and 58 percent of women, respectively. The LEFt clinical prediction rule was further validated in a separate cohort of 157 pregnant women with suspected DVT [76]. In this population, a negative LEFt rule accurately identified all women (29 percent) who did not have a DVT. The rule should not be used as a stand-alone test for excluding DVT and needs further prospective validation in a larger population before it can be routinely applied in clinical practice.

D-dimer — Due to the natural rise in levels with each trimester, D-dimer using a cut-off value of >500 ng/mL (by enzyme-linked immunosorbent assay [ELISA] or RBC agglutination [SimpliRED])

has limited value as a pretest probability tool for the diagnosis of DVT in pregnancy [57-60]. However, a negative test (<500 ng/mL), when present, can significantly lower the clinical suspicion for DVT and aid the physician in the decision to avoid further testing (algorithm 1) [58,73]. Moderate to high sensitivity D-dimer testing (ie, a higher cut-off value) is not validated in pregnancy and cannot be routinely used as a pretest probability tool for the diagnosis of suspected DVT in pregnancy. Studies describing the use of D-dimer in pregnancy are discussed in detail separately. (See 'D-dimer' above.)

Compressive ultrasound and subsequent testing — All pregnant patients suspected of having a DVT should undergo initial evaluation with compressive ultrasound (CUS) (algorithm 1). Proximal CUS is preferred as the first-line test for the diagnosis of suspected DVT in pregnancy over venography or magnetic resonance imaging [73]. In advanced pregnancy, CUS should be performed with the patient in the left lateral decubitus position.

The need for additional testing (eg, Doppler ultrasound of the iliac vein, magnetic resonance, or contrast venography) is dependent upon the CUS results and clinical suspicion (algorithm 1).

Positive CUS — A positive CUS is diagnostic of DVT. Anticoagulation should be initiated. The benefits of anticoagulation for DVT outweigh the bleeding risks during pregnancy or the puerperium. (See 'Imaging' above and "Deep vein thrombosis and pulmonary embolism in pregnancy: Treatment".)

Negative CUS — A negative CUS does not rule out DVT in the pregnant patient. Further testing depends upon the degree of clinical suspicion. When the initial CUS is negative, but clinical suspicion for DVT remains, there are two reasonable options: further testing concurrent with empiric anticoagulation, or further testing with anticoagulation reserved for confirmed cases on follow-up testing. There is a paucity of data to guide the clinician with this decision. The clinician is reliant upon judgment and should weigh the risks of untreated venous thromboembolism (VTE) and bleeding in a pregnant patient in the context of clinical suspicion (algorithm 1). In general, the following apply:

- When the clinical suspicion is high (eg, suspected iliac vein thrombosis with swelling of the entire leg and buttock), we prefer further evaluation with Doppler ultrasound directed at the iliac vein, followed by magnetic resonance or contrast venography, as needed. For these patients, we suggest empiric anticoagulation. This preference places a high value on diagnostic certainty and risk of maternal death for an untreated thrombosis in pregnancy, and places less value on risk of radiation or contrast exposure. (See 'Imaging' above.)

- For patients in whom the clinical suspicion is not high, we prefer serial CUS (performed on day 3 and 7) without empiric anticoagulation but with clinical follow-up throughout pregnancy. Data from nonpregnant [62,64,73] and pregnant patients [58,65-67,73] suggest that the safety of withholding anticoagulation in this setting is assured. This preference places a high value

on avoiding unnecessary anticoagulation when the risk of DVT is low. If serial CUS is not feasible, we suggest measuring D-dimer levels as an alternative. When D-dimer is <500 ng/mL (by ELISA or SimpliRED), DVT is unlikely [58]. (See 'Serial compression ultrasonography' above.)

There is no measureable radiation exposure associated with ultrasound or magnetic resonance imaging. However there are risks to the fetus and mother associated with radiation exposure for contrast venography, and with iodinated and gadolinium contrast for venographic studies. The risks of radiation exposure and contrast administration during pregnancy are discussed in detail separately. (See "Pulmonary embolism in pregnancy: Epidemiology, pathogenesis, and diagnosis", section on 'Radiation and contrast exposure'.)

DIAGNOSIS

The diagnosis of deep vein thrombosis (DVT) in pregnancy is made by demonstrating a lack of compressibility of the proximal veins on compressive ultrasound (femoral vein thrombosis) or poor flow on Doppler imaging of the femoral-iliac vein (iliac vein thrombosis). The diagnosis is rarely made by the demonstration of a filling defect on contrast or magnetic resonance venography. D-dimer levels and clinical exam cannot be used alone to diagnose DVT. A diagnostic approach for suspected DVT in pregnancy is discussed in detail above (algorithm 1). (See 'Diagnostic algorithm' above.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of DVT in pregnancy is similar to that in non-pregnant patients. It includes other entities that present with erythema, warmth, swelling and tenderness of the lower extremity and/or flank, lower abdomen, buttock, or back. However, the clinical signs and symptoms of DVT in pregnancy are masked by many of the physiologic changes of normal pregnancy (eg, lower extremity swelling and cramping).

The clinical suspicion for DVT should be high in the setting of pregnancy. Although not always present, features that are highly suggestive of the diagnosis include unilateral signs and symptoms and the classic symptoms of iliac vein thrombosis (flank/pelvic/buttock pain and swelling). Such symptoms should prompt immediate investigation for DVT with compressive or Doppler ultrasound. It is important to note that DVT can coexist with other conditions. Thus, although the finding of an alternative diagnosis (eg, cellulitis) will lower the clinical suspicion for DVT, it does not always obviate the need for diagnostic imaging.

The differential diagnosis of DVT in nonpregnant patients and the physiologic changes of pregnancy that can mimic DVT are discussed separately. (See "Maternal adaptations to

pregnancy: Cardiovascular and hemodynamic changes" and "Clinical presentation and diagnosis of the nonpregnant adult with suspected deep vein thrombosis of the lower extremity".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Superficial vein thrombosis, deep vein thrombosis, and pulmonary embolism" and "Society guideline links: Anticoagulation in pregnancy".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Deep vein thrombosis (blood clots in the legs) (The Basics)")
- Beyond the Basics topics (see "Patient education: Deep vein thrombosis (DVT) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Venous thromboembolism (VTE) can manifest during pregnancy as an isolated lower extremity deep venous thrombosis (DVT) or pulmonary embolus (PE). PE is the seventh leading cause of maternal mortality, responsible for 9 percent of maternal deaths. (See 'Epidemiology' above.)
- Pregnancy is a risk factor for the development of VTE with a reported incidence that is 4 to 50 times higher in pregnant women compared to nonpregnant women. Increased risk for lower

extremity DVT is highest in the first six weeks of the postpartum period, with a higher than usual incidence of left-sided DVT and pelvic vein clot. (See 'Risk factors' above.)

- Signs and symptoms suggestive of proximal vein thrombosis are diffuse pain and swelling that may or may not be associated with erythema, warmth and tenderness of the lower extremity. Symptoms of iliac vein thrombosis include swelling of the entire leg with or without flank, lower abdomen, buttock, or back pain.

- The clinical features of DVT in pregnancy overlap with many of the features of normal pregnancy. A high index of clinical suspicion and low threshold for the use of objective confirmatory testing are required to accurately diagnose DVT during pregnancy. (See 'Clinical presentation' above and 'Diagnostic algorithm' above.)

- D-dimer and clinical prediction rules are of limited value as pretest probability tools for the diagnosis of DVT during pregnancy and the puerperium. Moderate or highly sensitive D-dimer (with higher than usual cut-off values) have not been adequately validated for routine use in pregnancy. However, a negative D-dimer is associated with a high negative predictive value in any trimester. (See 'Laboratory testing' above and 'Pretest probability' above.)

- The diagnosis of DVT in pregnancy is made by demonstrating a lack of compressibility of the proximal veins on compressive ultrasound (femoral vein thrombosis) or poor flow on Doppler imaging of the femoral-iliac vein (iliac vein thrombosis). The diagnosis is rarely made by the demonstration of a filling defect on contrast or magnetic resonance venography. D-dimer levels and clinical exam cannot be used alone to diagnose DVT. (See 'Diagnosis' above.)

- Our approach to the evaluation of a patient with suspected DVT in pregnancy depends at least partially upon the degree of clinical suspicion (algorithm 1).

- For all pregnant patients suspected of having a lower extremity DVT, we recommend proximal vein compression ultrasound (CUS) with the patient in the left lateral decubitus position as the first-line diagnostic test, over venography or magnetic resonance imaging (algorithm 1). (See 'Compressive ultrasound and subsequent testing' above.)

- For pregnant patients with a negative CUS in whom the clinical suspicion is not high, we suggest serial CUS performed on day 3 and day 7 with additional clinical observation for the duration of pregnancy. (See 'Compressive ultrasound and subsequent testing' above.)

- For pregnant patients with a negative CUS in whom the clinical suspicion is high, particularly those with signs and symptoms of iliac vein thrombosis (pain and swelling of the entire leg and buttock), we suggest Doppler ultrasound directed at the iliac vein rather than magnetic resonance or contrast venography. (See 'Compressive ultrasound and subsequent testing' above.)

ACKNOWLEDGMENT

The editorial staff at UpToDate would like to acknowledge David R Schwartz, MD, who contributed to an earlier version of this topic review.

REFERENCES

1. Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. N Engl J Med 2008; 359:2025.
2. Greer IA. Thrombosis in pregnancy: maternal and fetal issues. Lancet 1999; 353:1258.
3. Prevention of venous thrombosis and pulmonary embolism. NIH Consensus Development. JAMA 1986; 256:744.
4. Kujovich JL. Hormones and pregnancy: thromboembolic risks for women. Br J Haematol 2004; 126:443.
5. Heit JA, Kobbervig CE, James AH, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005; 143:697.
6. Morris JM, Algert CS, Roberts CL. Incidence and risk factors for pulmonary embolism in the postpartum period. J Thromb Haemost 2010; 8:998.
7. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol 2006; 194:1311.
8. Bourjeily G, Paidas M, Khalil H, et al. Pulmonary embolism in pregnancy. Lancet 2010; 375:500.
9. Brown HL, Hiett AK. Deep vein thrombosis and pulmonary embolism in pregnancy: diagnosis, complications, and management. Clin Obstet Gynecol 2010; 53:345.
10. Arya R. How I manage venous thromboembolism in pregnancy. Br J Haematol 2011; 153:698.
11. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance--United States, 1991--1999. MMWR Surveill Summ 2003; 52:1.

12. The National Institute for Clinical Excellence. Why mothers die 2000–2002 — report on confi dential enquiries into maternal deaths in the United Kingdom. London: Royal College of Obst etricians and Gynaecologists Press, 2003.

13. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving mothers' lives: r eviewing maternal deaths to make motherhood safer — 2003–2005: the seventh report on c onfidential enquiries into maternal deaths in the United Kingdom. London: CEMACH, 2007.

14. Sultan AA, West J, Grainge MJ, et al. Development and validation of risk prediction model for venous thromboembolism in postpartum women: multinational cohort study. BMJ 2016; 355:i6253.

15. Simpson EL, Lawrenson RA, Nightingale AL, Farmer RD. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. BJOG 2001; 108:56.

16. McColl MD, Ramsay JE, Tait RC, et al. Risk factors for pregnancy associated venous thromboembolism. Thromb Haemost 1997; 78:1183.

17. Sachs BP, Brown DA, Driscoll SG, et al. Maternal mortality in Massachusetts. Trends and prevention. N Engl J Med 1987; 316:667.

18. MacKAy AP, Berg CJ, Liu X, et al. Changes in pregnancy mortality ascertainment: United States, 1999-2005. Obstet Gynecol 2011; 118:104.

19. http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html (Accessed on Novem ber 15, 2013).

20. Blondon M, Harrington LB, Righini M, et al. Racial and ethnic differences in the risk of postpartum venous thromboembolism: a population-based, case-control study. J Thromb Haemost 2014; 12:2002.

21. Treffers PE, Huidekoper BL, Weenink GH, Kloosterman GJ. Epidemiological observations of thrombo-embolic disease during pregnancy and in the puerperium, in 56,022 women. Int J Gynaecol Obstet 1983; 21:327.

22. Ghaji N, Boulet SL, Tepper N, Hooper WC. Trends in venous thromboembolism among pregnancy-related hospitalizations, United States, 1994-2009. Am J Obstet Gynecol 2013; 209:433.e1.

23. Ginsberg JS, Brill-Edwards P, Burrows RF, et al. Venous thrombosis during pregnancy: leg and trimester of presentation. Thromb Haemost 1992; 67:519.

24. Rutherford S, Montoro M, McGehee W, Strong T. Thromboembolic disease associated with pregnancy: an 11-year review. Am J Obstet Gynecol 1991; 164(Suppl):286.

25. Kierkegaard A. Incidence and diagnosis of deep vein thrombosis associated with pregnancy. Acta Obstet Gynecol Scand 1983; 62:239.

26. Stein PD, Hull RD, Kayali F, et al. Venous thromboembolism in pregnancy: 21-year trends. Am J Med 2004; 117:121.

27. Gherman RB, Goodwin TM, Leung B, et al. Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy. Obstet Gynecol 1999; 94:730.

28. Sultan AA, West J, Tata LJ, et al. Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. Br J Haematol 2012; 156:366.

29. Sultan AA, Tata LJ, West J, et al. Risk factors for first venous thromboembolism around pregnancy: a population-based cohort study from the United Kingdom. Blood 2013; 121:3953.

30. Abdul Sultan A, West J, Tata LJ, et al. Risk of first venous thromboembolism in pregnant women in hospital: population based cohort study from England. BMJ 2013; 347:f6099.

31. Kamel H, Navi BB, Sriram N, et al. Risk of a thrombotic event after the 6-week postpartum period. N Engl J Med 2014; 370:1307.

32. Tepper NK, Boulet SL, Whiteman MK, et al. Postpartum venous thromboembolism: incidence and risk factors. Obstet Gynecol 2014; 123:987.

33. Abdul Sultan A, Grainge MJ, West J, et al. Impact of risk factors on the timing of first postpartum venous thromboembolism: a population-based cohort study from England. Blood 2014; 124:2872.

34. Blondon M, Casini A, Hoppe KK, et al. Risks of Venous Thromboembolism After Cesarean Sections: A Meta-Analysis. Chest 2016; 150:572.

35. Haemostasis and Thrombosis Task Force, British Committee for Standards in Haematology. Investigation and management of heritable thrombophilia. Br J Haematol 2001; 114:512.

36. Chan WS, Spencer FA, Ginsberg JS. Anatomic distribution of deep vein thrombosis in pregnancy. CMAJ 2010; 182:657.

37. Cockett FB, Thomas ML, Negus D. Iliac vein compression.--Its relation to iliofemoral thrombosis and the post-thrombotic syndrome. Br Med J 1967; 2:14.

38. Hull RD, Raskob GE, Carter CJ. Serial impedance plethysmography in pregnant patients with clinically suspected deep-vein thrombosis. Clinical validity of negative findings. Ann Intern Med 1990; 112:663.

39. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 1998; 129:1044.

40. Friederich PW, Sanson BJ, Simioni P, et al. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis. Ann Intern Med 1996; 125:955.

41. 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; 179:1324.

42. Dizon-Townson DS, Nelson LM, Jang H, et al. The incidence of the factor V Leiden mutation in an obstetric population and its relationship to deep vein thrombosis. Am J Obstet Gynecol 1997; 176:883.

43. Gerhardt A, Scharf RE, Beckmann MW, 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.

44. Bergrem A, Dahm AE, Jacobsen AF, et al. Differential haemostatic risk factors for pregnancy-related deep-vein thrombosis and pulmonary embolism: a population-based case-control study. Thromb Haemost 2012; 108:1165.

45. Zotz RB, Gerhardt A, Scharf RE. Inherited thrombophilia and gestational venous thromboembolism. Best Pract Res Clin Haematol 2003; 16:243.

46. Branch DW, Silver RM, Blackwell JL, et al. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynecol 1992; 80:614.

47. GOODRICH SM, WOOD JE. PERIPHERAL VENOUS DISTENSIBILITY AND VELOCITY OF VENOUS BLOOD FLOW DURING PREGNANCY OR DURING ORAL CONTRACEPTIVE THERAPY. Am J Obstet Gynecol 1964; 90:740.

48. Wright H, Osborn S, Edmunds D. Changes in the rate of flow of venous blood in the leg during pregnancy, measured with radioactive sodium. Surg Gynecol Obstet 1950; 90:481.

49. Macklon NS, Greer IA, Bowman AW. An ultrasound study of gestational and postural changes in the deep venous system of the leg in pregnancy. Br J Obstet Gynaecol 1997; 104:191.

50. Hellgren M, Blombäck M. Studies on blood coagulation and fibrinolysis in pregnancy, during delivery and in the puerperium. I. Normal condition. Gynecol Obstet Invest 1981; 12:141.

51. Walker MC, Garner PR, Keely EJ, et al. Changes in activated protein C resistance during normal pregnancy. Am J Obstet Gynecol 1997; 177:162.

52. Bergrem A, Dahm AE, Jacobsen AF, et al. Resistance to activated protein C is a risk factor for pregnancy-related venous thrombosis in the absence of the F5 rs6025 (factor V Leiden) polymorphism. Br J Haematol 2011; 154:241.

53. Kruithof EK, Tran-Thang C, Gudinchet A, et al. Fibrinolysis in pregnancy: a study of plasminogen activator inhibitors. Blood 1987; 69:460.

54. Gerbasi FR, Bottoms S, Farag A, Mammen E. Increased intravascular coagulation associated with pregnancy. Obstet Gynecol 1990; 75:385.

55. Lee RV, McComb LE, Mezzadri FC. Pregnant patients, painful legs: the obstetrician's dilemma. Obstet Gynecol Surv 1990; 45:290.

56. Bergqvist A, Bergqvist D, Hallböök T. Deep vein thrombosis during pregnancy. A prospective study. Acta Obstet Gynecol Scand 1983; 62:443.

57. Kline JA, Williams GW, Hernandez-Nino J. D-dimer concentrations in normal pregnancy: new diagnostic thresholds are needed. Clin Chem 2005; 51:825.

58. Chan WS, Chunilal S, Lee A, et al. A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy. Ann Intern Med 2007; 147:165.

59. Chan WS, Lee A, Spencer FA, et al. D-dimer testing in pregnant patients: towards determining the next 'level' in the diagnosis of deep vein thrombosis. J Thromb Haemost 2010; 8:1004.

60. Kovac M, Mikovic Z, Rakicevic L, et al. The use of D-dimer with new cutoff can be useful in diagnosis of venous thromboembolism in pregnancy. Eur J Obstet Gynecol Reprod Biol 2010; 148:27.

61. Polak JF, Wilkinson DL. Ultrasonographic diagnosis of symptomatic deep venous thrombosis in pregnancy. Am J Obstet Gynecol 1991; 165:625.

62. Lohr JM, Kerr TM, Lutter KS, et al. Lower extremity calf thrombosis: to treat or not to treat? J Vasc Surg 1991; 14:618.

63. Wells PS, Hirsh J, Anderson DR, et al. Comparison of the accuracy of impedance plethysmography and compression ultrasonography in outpatients with clinically suspected deep vein thrombosis. A two centre paired-design prospective trial. Thromb Haemost 1995; 74:1423.

64. Heijboer H, Cogo A, Büller HR, et al. Detection of deep vein thrombosis with impedance plethysmography and real-time compression ultrasonography in hospitalized patients. Arch Intern Med 1992; 152:1901.

65. Chan WS, Spencer FA, Lee AY, et al. Safety of withholding anticoagulation in pregnant women with suspected deep vein thrombosis following negative serial compression ultrasound and iliac vein imaging. CMAJ 2013; 185:E194.

66. Le Gal G, Prins AM, Righini M, et al. Diagnostic value of a negative single complete compression ultrasound of the lower limbs to exclude the diagnosis of deep venous thrombosis in pregnant or postpartum women: a retrospective hospital-based study. Thromb Res 2006; 118:691.

67. Raţiu A, Navolan D, Spătariu I, et al. Diagnostic value of a negative single color duplex ultrasound in deep vein thrombosis suspicion during pregnancy. Rev Med Chir Soc Med Nat Iasi 2010; 114:454.

68. Carpenter JP, Holland GA, Baum RA, 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.

69. Spritzer CE, Evans AC, Kay HH. Magnetic resonance imaging of deep venous thrombosis in pregnant women with lower extremity edema. Obstet Gynecol 1995; 85:603.

70. Torkzad MR, Bremme K, Hellgren M, et al. Magnetic resonance imaging and ultrasonography in diagnosis of pelvic vein thrombosis during pregnancy. Thromb Res 2010; 126:107.

71. Hull R, Hirsh J, Sackett DL, et al. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation 1981; 64:622.

72. Lensing AW, Büller HR, Prandoni P, et al. Contrast venography, the gold standard for the diagnosis of deep-vein thrombosis: improvement in observer agreement. Thromb Haemost 1992; 67:8.

73. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e351S.

74. ACOG Practice Bulletin No. 196 Summary: Thromboembolism in Pregnancy. Obstet Gynecol 2018; 132:243.

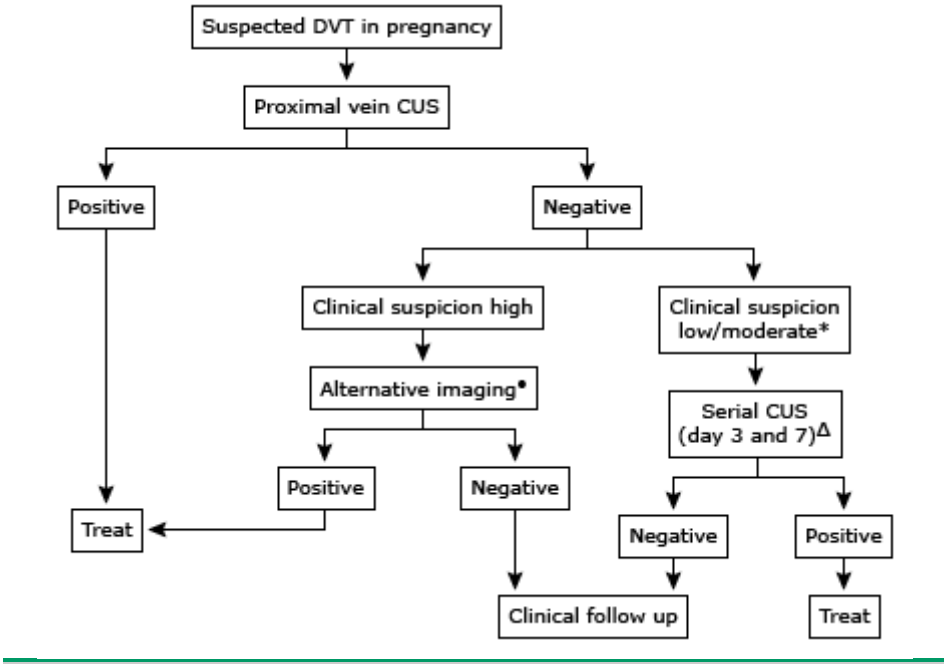
75. Chan WS, Lee A, Spencer FA, et al. Predicting deep venous thrombosis in pregnancy: out in "LEFt" field? Ann Intern Med 2009; 151:85.

76. Righini M, Jobic C, Boehlen F, et al. Predicting deep venous thrombosis in pregnancy: external validation of the LEFT clinical prediction rule. Haematologica 2013; 98:545.

Topic 1349 Version 41.0

GRAPHICS

Diagnostic algorithm for suspected deep venous thrombosis in pregnancy



CUS: compression ultrasound.
* Refers to patients with an initial negative CUS in whom clinical suspicion remains that is not high. Refer to UpToDate topics on deep vein thrombosis in pregnancy.
• Alternative imaging techniques include doppler ultrasound of the iliac vein and contrast or magnetic resonance venography.
Δ Consideration can be given to measuring a D-dimer level using enzyme linked immunosorbent assay (ELISA) or red blood cell agglutination (SimpliRED). A D-dimer level <500 ng/mL is considered negative and no further testing is needed. A D-dimer level >500 ng/mL is not diagnostic and has no value in directing further testing in pregnant women.

Graphic 90286 Version 1.0

Contributor Disclosures

Atul Malhotra, MD Consultant/Advisory Boards: Alfred Mann Foundation. Other Financial Interest: ResMed [philanthropic donation to UCSD]. **Steven E Weinberger, MD** Nothing to disclose **Lawrence LK Leung, MD** Nothing to disclose **Charles J Lockwood, MD, MHCM** Nothing to disclose **Jess Mandel, MD** Nothing to disclose **Geraldine Finlay, MD** Consultant/Advisory Boards: LAM Board of directors, LAM scientific grant review committee for The LAM Foundation.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy