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## Venous Thromboembolism during Pregnancy and the Postpartum Period: Risk Factors, Diagnostic Testing, and Treatment

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### Abstract

**Importance:** The risk of venous thromboembolism (VTE) increases during pregnancy and the postpartum period. Deep vein thrombosis (DVT) is the most common VTE during pregnancy, but pulmonary embolism (PE) is typically of greater concern as it contributes to far higher morbidity and mortality. Diagnosis and treatment of VTE during pregnancy differs substantially from the general nonpregnant population.

**Objective:** This review describes the epidemiology, risk factors, clinical presentation, diagnosis, and treatment of VTE during pregnancy and the postpartum period.

**Evidence Acquisition:** First, we reviewed VTE guidelines from professional societies in obstetrics, cardiology, hematology, emergency medicine, pulmonology, and critical care. Second, we examined references from these documents and used PubMed to identify recent articles that cited the guidelines. Finally, we searched PubMed and Google Scholar for articles published since 2019 that included terms for pregnancy and the epidemiology, risk factors, diagnostic imaging, or treatment of VTE.

**Results:** VTE risk increases throughout pregnancy and peaks shortly after delivery. More than half of pregnancy-related VTE are associated with thrombophilia; other major risks include

cesarean delivery, postpartum infection, and the combination of obesity with immobilization. Most VTE can be treated with low-molecular weight heparin, but cases of limb- or life-threatening VTE require consideration of thrombolysis and other reperfusion therapies.

**Conclusions and Relevance:** VTE is far more frequent in antepartum and postpartum women than age-matched controls, and clinical suspicion for VTE in this population should incorporate pregnancy-specific risks. Treatment of limb- or life-threatening antepartum or postpartum VTE requires multispecialty coordination to optimize maternal and fetal outcomes.

**Target Audience:**

general obstetricians; perinatologists; emergency physicians; family physicians

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## INTRODUCTION

Venous thromboembolism (VTE) is a major cause of morbidity and mortality during pregnancy and the postpartum period. Deep vein thrombosis (DVT) represents the majority of pregnancy-associated VTE, but pulmonary embolism (PE) is often of greater concern as it causes the majority of VTE-related morbidity and contributes to 10–15% of pregnancy-associated maternal deaths in high-income countries.<sup>1,2</sup> Given this burden of disease, VTE is a frequent diagnostic consideration among clinicians caring for pregnant patients, yet it presents a diagnostic dilemma due to the overlap of pathologic signs and symptoms with those of normal pregnancy.

The objective of this narrative review is to assist providers that care for pregnant and postpartum patients by summarizing critical elements from recent literature on the epidemiology, clinical features, diagnosis, and treatment of VTE in this population.

## EPIDEMIOLOGY

Pregnancy is among the most common hypercoagulable conditions in the general population. This physiologic change is attributable to increased levels of coagulation factors (including factors V, VII, VIII, X, XII, fibrinogen, and von Willebrand factor),<sup>3–5</sup> decreased free levels and activity of protein S,<sup>3</sup> and acquired resistance to activated protein C.<sup>5</sup> Fibrinolytic activity declines during pregnancy due to increased production of plasminogen activator inhibitor types 1 and 2 (PAI-1, PAI-2).<sup>4</sup> Hormone-mediated venodilation starts in the first trimester, and the resulting venous stasis is exacerbated by uterine compression of pelvic veins and the inferior vena cava later in pregnancy.<sup>6</sup>

Pregnant women experience 10–14 VTE events per 10,000 deliveries.<sup>7–9</sup> Incidence of VTE increases slightly above that of the general population in the first trimester, rises to a greater degree during the third trimester,<sup>10–13</sup> and peaks in the first two weeks after delivery.<sup>10,12,14,15</sup> Approximately half of all pregnancy-associated VTEs occur postpartum.<sup>8,16</sup> Most of these events occur within six weeks after delivery,<sup>10–12</sup> although the VTE risk remains elevated for up to 12 weeks.<sup>17</sup> The longer antepartum interval has an overall lower incidence rate (6.5 VTE / 10,000 person-years [PY]) than the 12 postpartum weeks (22.9 VTE/10,000 PY).<sup>15</sup> Compared to similarly aged nonpregnant controls, the daily

risk of VTE in antepartum and postpartum women is 3–10 times higher and 12–35 times higher, respectively.<sup>10,15,18,19</sup>

## RISK FACTORS

Major non-obstetric risk factors for VTE in the general population include older age, lower extremity fractures, orthopedic surgery, major trauma, cancer, and cardiac disease,<sup>20</sup> yet these are uncommon among most pregnant patients. Pregnancy-associated risk factors for VTE include cesarean delivery,<sup>8,21–23</sup> assisted reproductive technology,<sup>22</sup> stillbirth,<sup>21</sup> preterm birth,<sup>21</sup> preeclampsia,<sup>22,24,25</sup> obstetric hemorrhage,<sup>21–23</sup> and postpartum infection.<sup>21–23</sup> Medical conditions associated antepartum or postpartum VTE include preexisting diabetes mellitus,<sup>21</sup> inflammatory bowel disease,<sup>21,26</sup> systemic lupus erythematosus,<sup>27</sup> and sickle cell disease.<sup>16,28</sup> Body mass index (BMI) is not consistently associated with antepartum VTE, but postpartum VTE occurs at higher rates in obese patients with BMI above 35 or with concurrent immobilization.<sup>21–23</sup> Table 1 displays published estimates of antepartum and postpartum VTE risk after multivariable regression to adjust for confounders.

### Personal History of VTE.

Between 4–25% of pregnancy-associated VTE are recurrent events.<sup>7,16</sup> In pregnant patients with prior VTE who do not receive thromboprophylaxis during pregnancy, the risk of VTE is nearly 100-fold higher (900–1200 VTE/10,000 deliveries) than among pregnant patients in general.<sup>8,29,30</sup> Women with prior VTE in the setting of pregnancy or estrogen use appear to have higher rates of recurrent VTE during pregnancy compared to women whose prior VTE was associated with non-hormonal risk factors or no known risk factors (“unprovoked”).<sup>19</sup> VTE prophylaxis in pregnancy is an important and complex clinical decision that is beyond the scope this review but is addressed in clinical practice guidelines.<sup>31–33</sup>

### Thrombophilias.

More than half of pregnancy-related VTEs are associated with an underlying thrombophilia.<sup>6,34</sup> (Table 2) These conditions include genetic mutations that modify the activity of clotting factors as well as prothrombotic conditions that result from deficiencies of endogenous anticoagulants. Factor V Leiden (FVL) and the prothrombin gene G20210A mutation (PGM) are the two most common inherited thrombophilias and are associated with 40 percent and 17 percent of pregnancy-associated VTE, respectively (Table 2).<sup>6,35</sup> The primary acquired thrombophilia is antiphospholipid syndrome (APS), which is found in 3–5% of the population and is associated with VTE, preeclampsia, and other adverse pregnancy outcomes.<sup>16</sup> It is highly probable that undiscovered genetic sequence variations increase clotting risk in pregnancy.

Other factors also influence VTE risk associated with thrombophilia. For example, FVL heterozygotes have a baseline VTE risk of roughly 0.8% (8 per 1,000 pregnancies), but the risk is higher among patients with family history of VTE (1.5%) or personal history of VTE (10%).<sup>6,34</sup> Each condition can also have varying degrees of severity. For example,

acquired antithrombin (AT) deficiency from medical comorbidities typically reduces AT function only slightly (70–90% of normal) and has a trivial impact on VTE risk,<sup>6,36</sup> whereas the nearly 400 mutations that can cause inherited AT deficiency may result in severely reduced AT activity (40–60% of normal) and produce an estimated 6.1–9.0% risk of antepartum or postpartum VTE.<sup>36,37</sup> Several society guidelines classify thrombophilias as low risk (heterozygous FVL or PGM; deficiency of protein C or protein S) or high risk (homozygous FVL or PGM; FVL-PGM compound heterozygote; inherited AT deficiency) to inform decisions on prophylaxis for antepartum and postpartum VTE, although there is not consensus on this classification.<sup>6,38,39</sup>

## CLINICAL PRESENTATION

### Deep vein thrombosis.

This review focuses on deep vein thromboses occur in the lower extremities, although upper extremity and ovarian vein thromboses may occur in the setting of a prothrombotic state such as pregnancy.

More than 80 percent of pregnant patients with DVT present with unilateral leg symptoms, of which calf tenderness and pitting edema are the most common.<sup>31,40</sup> A calf circumference difference of at least 2 cm is significantly associated with DVT diagnosis.<sup>40</sup> A slight majority of lower extremity DVTs (58%) in the general population occur in the left leg, a propensity linked to left iliac vein compression by the right iliac artery (May-Thurner Syndrome), an anatomical variant found in 22–24% of the population.<sup>41</sup> This left-sided predominance is even greater during pregnancy, potentially as a result of left iliac vein compression by the gravid uterus, as 88% of all DVTs and 95% of iliofemoral DVTs during pregnancy are diagnosed in the left leg.<sup>42</sup> Pregnant women with left leg symptoms are 17 times more likely to be diagnosed with DVT than pregnant women with right-sided or bilateral lower extremity symptoms.<sup>40</sup> Since physiologic lower extremity edema is common during the second and third trimesters, women who develop symptoms concerning for DVT during the first trimester are far more likely (OR = 53) to be diagnosed with DVT compared to women who develop symptoms later in pregnancy.<sup>40</sup> Compared to the general population, pregnant patients have a slightly higher proportion of DVTs located in iliofemoral vessels (64% vs. 54%) and a much higher proportion of DVTs isolated to the iliac vein (17% vs 3%), both of which are associated with higher risks of embolization.<sup>42–44</sup> Patients with iliac vein thrombosis may present with swelling of the entire leg and may have associated pain of the flank, back, hip, or buttock.<sup>31</sup> As a result, pregnant patients with DVT may have symptoms that start in the thigh or buttock, rather than having more “traditional” symptoms that start distally and extend proximally.

### Pulmonary embolism.

Routine physiologic changes of pregnancy often produce dyspnea, lower extremity edema, and resting tachycardia that mimic signs and symptoms of pulmonary embolism, thereby presenting a challenge for physicians to assess the presence of PE based on clinical factors alone. For example, among pregnant and postpartum women tested for PE in the DiPEP study, those with PE had similar rates of pleuritic chest pain (52%), dyspnea (54%),

palpitations (13%), cough (8%), and syncope (5%) compared to women without PE.<sup>45</sup> In that study, variables associated with PE included older age, lower oxygen saturation, lower systolic blood pressure, and temperature; however, these continuous variables often provide little value for distinguishing PE from other common conditions on the basis of physical exam alone. Furthermore, many patients with PE have normal vital signs. For instance, two-thirds of pregnant and postpartum women with PE in the multinational RIETE registry had initial peripheral oxygen saturations above 95%.<sup>46</sup> Only 7% of antepartum women and 1.4% of postpartum women in the RIETE registry presented with hypotension, the most ominous vital sign indicator of PE severity.

## DIAGNOSTIC TESTING

### Laboratory Testing

D-dimer assays are routinely used in non-pregnant patients to rule out VTE, particularly PE, but the utility of d-dimer during pregnancy is less clear. D-dimer levels increase with gestational age and are therefore much less specific for VTE, particularly in late pregnancy.<sup>47</sup> Based on low-quality evidence, several obstetrical society guidelines published between 2011–2018 discouraged d-dimer testing in pregnancy due its low specificity.<sup>31,48–51</sup> The 2019 Artemis study (discussed below) evaluated pregnant patients with d-dimer using one of two different thresholds based on a patient's symptoms and the physician's clinical impression; among 195 patients (39% of cohort) who avoided PE imaging based on negative d-dimer results, there was one diagnosis of DVT and no diagnosis of PE during 3 months of clinical follow-up.<sup>52</sup> Based on these results, the 2019 European Society of Cardiology (ESC) guidelines state that d-dimer measurement should be considered to rule out PE in pregnant or postpartum patients (*Class IIa, Level B*).<sup>20</sup>

### Diagnostic Imaging

**Imaging for DVT**—Guidelines published by the American College of Chest Physicians (ACCP) in 2012 and affirmed by ACOG in 2018 recommended that pregnant patients with suspected DVT should first undergo compression ultrasound (CUS) of the proximal veins (i.e., femoral and popliteal veins)(*ACCP Grade 2C*),<sup>31,53</sup> while some organizations recommend whole-leg venous compression ultrasound.<sup>44,50</sup> Pregnant patients with normal proximal CUS results should have dedicated iliac vein testing (typically Doppler/duplex ultrasonography or rarely non-contrast MRI) if they have symptoms of iliac vein DVT, such as swelling of the entire leg or pain along the back, buttock, or flank (*ACCP Grade 2C*).<sup>31,33,50,51,53</sup> Providers should consider repeat testing in 3 days and 7 days for patients with negative initial results (*ACCP Grade 1B*).<sup>31,51,53</sup> Other approaches include high-sensitivity d-dimer testing after initial negative proximal CUS if there is no concern for iliac DVT (*ACCP Grade 2B*).<sup>53</sup>

**Imaging for PE**—Lung ventilation/perfusion scintigraphy (V/Q scan) and computed tomography pulmonary angiography (CTPA) are widely used for evaluation of PE in pregnancy, and both are discussed in detail below.<sup>20,31,33,50,51</sup> Ventilation-perfusion single photon emission CT (V/Q SPECT) is a promising technique that offers greater sensitivity and lower rates of nondiagnostic testing compared to planar V/Q while requiring a

lower radiation dose than CTPA;<sup>20</sup> however, it remains uncommon in the US despite significant adoption in other industrialized nations.<sup>54</sup> Unenhanced magnetic resonance (MR) angiography for PE is discouraged due to poor sensitivity in general patient populations, and enhanced MR imaging is contraindicated in pregnancy due to fetal risks from gadolinium-based contrast agents.<sup>49,55,56</sup>

**Lung scintigraphy (V/Q Scan).**—Planar lung ventilation/perfusion scintigraphy was a common test for nonpregnant adults with suspected PE until the late 1990s, and it remains a common test in pregnancy. Most young pregnant women do not have significant lung disease, and guidelines support the use of perfusion-only scintigraphy (i.e., no ventilation scan) in pregnant patients with normal chest radiographs to reduce maternal and fetal radiation exposure.<sup>20,44,49–51,56</sup> V/Q scans can be used in patients with contraindications to CTPA, such as advanced kidney disease or anaphylactic reactions to iodinated contrast, but should be avoided in patients with asthma or chronic lung disease. Disadvantages of V/Q scan include limited availability at some centers, a longer time required to complete the test, a slightly higher fetal radiation dose, and an inability to identify alternative diagnoses (i.e., if the result is indeterminant or negative for PE).

**CTPA.**—In the US, CTPA has become the PE diagnostic imaging standard in nonpregnant patients since it is widely available, can provide rapid results, and has greater sensitivity and specificity for PE than planar V/Q in general patient populations.<sup>57</sup> Unlike scintigraphy, CTPA can often diagnose other acute conditions (i.e., pneumonia, aspiration, rib fracture) that may be responsible for patients' symptoms, and it can inform PE severity assessment by identifying signs of right ventricular (RV) dysfunction.<sup>20,58</sup> Pregnant patients more often have suboptimal CTPA vessel opacification than nonpregnant patients,<sup>44</sup> especially in the second and third trimesters, a difference attributed to flow artifacts resulting from the increased cardiac output of pregnancy. Protocols to increase the volume and injection rate of iodinated contrast may help improve study quality.<sup>49,56</sup> Fetal radiation dose from CTPA is slightly lower than from V/Q scan, but maternal breast radiation dose is higher. CTPA is contraindicated in patients with anaphylaxis to iodinated contrast and should generally be avoided in patients with severe kidney disease. Excess maternal iodine exposure presents a risk of fetal hypothyroidism,<sup>59</sup> but contemporary (i.e., water soluble, low-osmolar) iodinated contrast is rapidly cleared from circulation and is not associated with significant fetal thyroid dysfunction.<sup>49,59</sup> Maternal iodinated contrast also presents no risk to breastfeeding infants, so there is no need for postpartum patients to “pump and dump” after CTPA.<sup>55</sup>

**Other Imaging.**—Several other imaging studies play a role in PE diagnosis and severity assessment:

- *Lower extremity ultrasound.* Several guidelines recommend initial CUS to assess for DVT in pregnant women with suspected PE who also have leg symptoms,<sup>20,49,51,60</sup> with advanced chest imaging reserved for patients with negative CUS results. Two other guidelines recommend initial CUS regardless of leg symptoms.<sup>44,48</sup>

- *Radiographs.* Chest x-rays are often used to guide the selection of advanced imaging for PE. Many guidelines recommend lung scintigraphy if the radiographs are normal and CTPA if they are abnormal.<sup>44,49–51,60</sup> ESC guidelines indicate that lung scintigraphy is reasonable if radiographs are normal and that CTPA is reasonable regardless of radiograph results (class IIa, level C).<sup>20</sup>
- *Echocardiography.* In hemodynamically unstable patients who cannot obtain emergent CTPA, echocardiographic evidence of right ventricular pressure overload strongly suggests the presence of PE in patients with high pretest probability and no other likely causes of RV dysfunction (class I, level C).<sup>20</sup> Echocardiographic identification of RV dysfunction in hemodynamically stable patients also contributes to PE severity assessment and helps inform treatment.

**Radiation Exposure**—Radiation from diagnostic imaging is an important consideration. Estimated mean fetal radiation doses from CTPA (0.05–0.3 mGy) are typically slightly lower than those from V/Q scan (0.17–0.4 mGy), but both are far below the 50–100 mGy deterministic threshold for fetal radiation complications and have very low estimated risk of excess cancer-related death during childhood (approximately 1 per 100,000).<sup>20,55,61–63</sup> Pregnant women may face a higher lifetime attributable risk of cancer from PE imaging compared to the fetus, particularly since breast tissue is extremely radiosensitive during pregnancy. Historically, CTPA delivered a much higher absorbed radiation dose to maternal breast tissue (20–66 mGy)<sup>61,64–67</sup> than V/Q scans (0.3–0.7 mGy).<sup>61,68</sup> Both technologies have improved; with modern dose-reduction techniques, CTPA deliver doses of 3–10 mGy,<sup>69–72</sup> while low-dose perfusion-only scintigraphy (Q scan) may deliver only 0.1–0.3 mGy.<sup>61,73</sup> While radiation comparison across studies is limited by numerous methodological differences, CTPA is estimated to deliver 20–136 times more radiation to the breasts than V/Q or perfusion-only scans.<sup>67,68,74</sup> Guidelines disagree on the clinical significance of this difference, with maternal lifetime attributable risks of cancer from CTPA reported between 0.03–0.2%.<sup>20,50</sup> The 2019 ESC guidelines suggest that “avoiding CTPA on the grounds of maternal cancer risk is therefore not justified.”<sup>20</sup>

Specific patient factors may influence selection of imaging. In patients with severe symptoms, hemodynamic instability, or factors that predispose them to other emergent thoracic conditions, the benefits of rapid imaging (i.e., CTPA) may easily exceed the theoretical risk from radiation. In contrast, physicians treating patients with non-severe symptoms may wish to consider factors other than test speed. For instance, breast radiation absorbed from CTPA may be up to four-fold higher in patients with obese BMI (>30.1) compared to low BMI (BMI <19.7),<sup>63</sup> and patients with BRCA1 and BRCA2 genes have a stronger association between radiation exposure and subsequent breast cancer, especially if exposed at a younger age.<sup>75</sup>

## CLINICAL DECISION RULES

In nonpregnant adults, guidelines recommend stratifying patients by pretest probability and using clinical decision tools to avoid diagnostic imaging in patients unlikely to have PE.



The most common approaches to assessing PE pretest probability in nonpregnant adults are the Wells Score and Revised Geneva Score,<sup>76,77</sup> both of which stratify patients into three pretest probability categories (high, intermediate, low). Patients at high probability undergo imaging, while patients in the latter two categories may avoid imaging if other tests or decision tools (i.e., d-dimer or PE Rule Out Criteria<sup>78</sup>) indicate their risk of PE is very low. More recently, the YEARS protocol used two d-dimer thresholds based on whether patients had risk factors for PE (signs of DVT; hemoptysis; or clinical suspicion of PE as the most likely diagnosis) and was also found to safely reduce imaging.<sup>79</sup>

Several guidelines published between 2011–2016 discouraged use of the Wells and Geneva tools because their derivation studies excluded pregnant patients and there is little prospective data validating the tools in pregnant patients.<sup>44,45,48–51,80–83</sup> Since those guidelines were published, however, two large prospective trials delivered the first high-quality research on this topic:

- Righini et al prospectively evaluated the Revised Geneva score in a multicenter cohort of 395 pregnant patients with suspicion of PE, defined as new-onset chest pain or shortness of breath without another obvious cause.<sup>84</sup> Women in the high-risk category had CUS followed by CTPA if no DVT was found, while women with low or intermediate-risk had initial d-dimer testing and continued to imaging if the d-dimer was elevated. Forty-six patients (11.6%) with low or intermediate risk and negative d-dimer were managed without imaging, and none of these patients experienced VTE during three months of follow-up.
- The Artemis study, published in 2109 by Van der Pol and colleagues, evaluated a pregnancy-adapted YEARS algorithm in a prospective international cohort of 498 patients.<sup>52</sup> A total of 195 patients (39% of cohort) avoided chest imaging based on YEARS criteria and d-dimer values; in three months of follow-up, one patient (0.51%) was diagnosed with DVT and no patients were diagnosed with PE. Two retrospective studies of this algorithm found similarly positive findings,<sup>85,86</sup> while a third retrospective study concluded this approach had insufficient sensitivity to safely rule out PE.<sup>87</sup>

While these studies show promise for reducing unnecessary imaging in pregnant patients, more high-quality studies are needed to validate and refine this approach.

## TREATMENT

Treatment of antepartum and postpartum VTE varies widely based on clot location, severity, timing in relation to delivery, and local institutional resources.

### DVT Treatment

**Pharmacotherapy.**—Whereas a majority of nonpregnant patients with acute DVT are treated with direct oral anticoagulants (DOACs) or vitamin K antagonists, both agents should be avoided in pregnancy as they cross the placenta and may be associated with adverse fetal outcomes.<sup>31–33,48,51</sup> Instead, low molecular weight heparin (LMWH) is generally favored over unfractionated heparin (UFH) as the first-line treatment for both

antepartum DVT and early postpartum DVT due to its greater bioavailability, longer anticoagulant effect, and lower rates of adverse effects (*ACCP Grade 1B*).<sup>20,32,51,88</sup> Guidelines recommend once- or twice-daily weight-adjusted LMWH dosing based on early pregnancy weight (Table 3). UFH is recommended in patients with renal failure (creatinine clearance < 30 ml/min) and should be considered in patients anticipated to have poor subcutaneous drug absorption (e.g., anasarca or severe obesity).<sup>20</sup> Warfarin may be used for postpartum DVT but DOACs remain contraindicated if breastfeeding.<sup>31,32</sup> Hospitalization may be considered for patient with large DVT clot burden or significant comorbidities.

**Inferior vena cava (IVC) filters.**—Several obstetric society guidelines suggest IVC filters should be considered in pregnant patients with recurrent VTE despite therapeutic anticoagulation.<sup>31,32,89</sup> The Royal College of Obstetricians and Gynecologists (RCOG) suggests IVC filters should also be considered during the peripartum period for patients with known iliac DVT.<sup>51</sup>

**Severe DVT.**—In rare cases, severe proximal lower extremity DVT with extensive venous obstruction may cause early arterial insufficiency (phlegmasia alba dolens), which typically presents with limb pallor, pain, and extensive swelling. This condition may progress to phlegmasia cerulea dolens,<sup>41</sup> which manifests with limb cyanosis and severe pain reflective of critical limb ischemia and venous gangrene. In general populations, anticoagulation alone is associated with poor outcomes for this limb-threatening condition, and treatment should include early thrombus removal using catheter-directed interventions.<sup>90</sup> For patients with contraindications to thrombolysis, open surgical venous thrombectomy is recommended.<sup>90</sup> Several society guidelines support consideration of thrombolysis in patients with limb-threatening ischemia from DVT.<sup>31,32,48</sup> Pregnant patients with severe proximal DVT who may warrant thrombolysis or thrombectomy should receive initial parenteral anticoagulation with UFH (Table 3), and individual patient decisions regarding definitive therapy should be guided by multispecialty local expertise and patient preferences.<sup>31,51,89</sup>

## PE Treatment

**PE risk stratification.**—Treatment of pulmonary embolism differs greatly based on assessment of PE severity (i.e., stratification of short-term mortality risk). We are aware of no pregnancy-specific criteria for assessment of PE severity. Guidelines from the ESC and the American Heart Association (AHA) recommend three-tier classification of PE severity based on hemodynamic status, cardiac dysfunction, and comorbidities. Although this approach to PE severity assessment has not been validated in pregnancy, literature suggests the criteria remain valid during physiologic changes of the antepartum period.<sup>91</sup>

- **High-risk (massive) PE.** Acute PE associated with cardiac arrest, shock with end-organ dysfunction, or persistent hypotension is associated with high short-term mortality risk in general adult patients (14–57%).<sup>20,92–94</sup> Fetal distress has been proposed as another end-organ criterion for defining high-risk PE in pregnancy.<sup>91</sup> High-risk PE represents 3.9% of acute PE (range 3.1–12%) in registry studies of general adult patients.<sup>94</sup> Approximately 7.0–7.3% of pregnant women with PE have hypotension at initial presentation,<sup>2,46</sup> while hypotension is noted in a smaller proportion (1.4%) of postpartum PEs.<sup>46</sup> Estimated in-hospital

mortality for high-risk antepartum PE (37%) is nearly 50 times higher than for hemodynamically stable antepartum PE (0.8%).<sup>2</sup>

- *Intermediate-risk (submassive) PE.* Normotensive patients with acute PE have intermediate mortality risk if they have evidence of myocardial necrosis (i.e., elevated serum troponin) or right ventricular dysfunction (i.e., based on imaging or elevated natriuretic peptides).<sup>20,92</sup> Patients may also have intermediate mortality risk based on advanced age, abnormal vital signs, or significant comorbidities as noted by the Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI).<sup>95,96</sup> Neither the PESI or sPESI has been prospectively evaluated in pregnancy.
- *Low-risk (nonmassive) PE.* Patients with acute PE with normal vital signs, normal cardiac function, and no significant medical comorbidities have low short-term mortality. Data from the international RIETE registry indicate that most pregnant (60%) and postpartum (67%) women with acute PE had normal sPESI scores and likely qualified as low-risk,<sup>46</sup> although some patients may have qualified as intermediate risk based on other criteria.

### Treatment of intermediate/low-risk (hemodynamically stable) PE

For patients with hemodynamically stable antepartum PE (i.e., intermediate or low risk), acute treatment includes anticoagulation with LMHW (or fondaparinux in the setting of heparin-induced thrombocytopenia) and hospitalization for hemodynamic monitoring. LMWH is generally preferred over UFH with exceptions as previously described for DVT. Patients with intermediate-risk PE may experience delayed hemodynamic decompensation; in the PEITHO (Pulmonary Embolism Thrombolysis) trial, nearly 7% of nonpregnant adults with intermediate-risk PE treated with anticoagulation alone experienced hemodynamic decompensation or all-cause mortality while hospitalized,<sup>97</sup> and these events occurred an average of 1.8 days (standard deviation 1.6 days) after diagnosis. Patients with low-risk PE are unlikely to decompensate, but pregnancy is generally considered a contraindication to outpatient-only PE management.<sup>98</sup> Low-risk PE beyond one week postpartum may be reasonable for brief observation or outpatient-only management based on patient circumstances.

### Treatment of high-risk (hemodynamically unstable) PE

Resuscitation and reperfusion of patients with severe cardiovascular compromise from acute PE requires multispecialty expertise and prompt mobilization of institutional resources (or coordinating an emergent transfer) to minimize morbidity and mortality.

**Oxygenation.**—Supplemental oxygen is recommended for patients with acute PE who have peripheral arterial oxygen saturation below 90%.<sup>20</sup> In high-risk PE, non-invasive ventilation such as high-flow nasal cannula is preferred over positive-pressure ventilation, as the latter may cause increased intrathoracic pressure which can worsen venous return and further impair cardiac output. Intubation should only be considered in patients who cannot tolerate noninvasive ventilation. If intubation becomes necessary, physicians should

use induction agents that are less likely to cause hypotension, and restraint should be used when applying positive end-expiratory pressure.<sup>20</sup>

**Hemodynamic support.**—In high-risk PE, hypotension is attributable to both (1) acute RV failure resulting in poor left ventricular preload and (2) reduction of cardiac output due to bowing of the interventricular septum into the left ventricle during early diastole. Initial hemodynamic support for patients with high-risk PE can include cautious intravascular volume loading (e.g., 500 mL crystalloid), but this approach can ultimately worsen RV distention, reduce LV filling, and decrease cardiac output.<sup>20</sup> Norepinephrine and dobutamine may be considered to improve cardiac output and coronary perfusion without worsening pulmonary vascular resistance (*ESC class IIa, level C*).<sup>20</sup>

**Anticoagulation.**—Guidelines recommend immediate parenteral anticoagulation for patients with hemodynamic instability due to suspected or known PE (*ESC class I, level C*).<sup>20,92</sup> Unfractionated heparin is specifically preferred in this setting as it may be discontinued if the PE diagnosis is confirmed and thrombolytic therapy is pursued (Table 3).<sup>20,89</sup> For hemodynamically stable antepartum patients with confirmed PE, LMWH is preferred over UFH as previously described regarding DVT.

**Reperfusion.**—Treatment of high-risk PE with systemic thrombolysis is recommended by guidelines as it is associated with lower short-term all-cause mortality (OR = 0.64–0.69) in nonpregnant adults (*ESC class I, level B; AHA class IIa, level B*) (Table 3).<sup>20,88,92,94,99</sup> Thrombolysis for high-risk antepartum PE is supported by multiple obstetric practice guidelines.<sup>20,31,33,48,51</sup> Two retrospective reviews found maternal survival rates of 57–94% following thrombolysis of pregnancy-associated high-risk PE.<sup>2,100</sup> Alteplase is approved by the US Food and Drug Administration (FDA) for thrombolysis of high-risk PE (Table 3) and is the most common agent used in this setting, whereas tenecteplase has a higher specificity for fibrin and a longer half-life but is not FDA-approved. In general nonpregnant patients, the AHA recommends withholding systemic anticoagulation during alteplase infusion and resuming it after the infusion, while the ESC recommends continuous UFH treatment during alteplase infusion.<sup>20,92</sup> We are aware of no trials comparing these approaches to anticoagulation during thrombolysis, and thrombolysis for high-risk PE should not be delayed if a patient received LMWH.

Major bleeding occurs after thrombolysis in approximately 18% of antepartum and 58% of postpartum women, with nearly all major postpartum bleeding occurring in patients who received thrombolysis within 72 hours after delivery.<sup>91,100</sup> Thrombolytics do not cross the placenta,<sup>48,89,91</sup> but obstetric complications may result from placental injury or the hemodynamic compromise of high-risk PE. Excluding cases of maternal death, thrombolysis for high-risk PE is associated with fetal and neonatal death rates of 12% and spontaneous labor rates of 19%.<sup>100</sup> Primary systemic thrombolysis is not recommended for general adult patients with intermediate- or low-risk PE (*ESC class III, level B*), but rescue thrombolysis is recommended for patients with PE who have subsequent hemodynamic deterioration despite anticoagulation treatment (*ESC class I, level B*).<sup>20</sup>

In patients with absolute contraindications to thrombolysis (prior hemorrhagic stroke; ischemic stroke within 6 months; intracranial arteriovenous malformation; malignant intracranial neoplasms; active bleeding; recent major trauma, surgery, or head injury) or refractory hemodynamic instability despite thrombolysis (i.e., failed thrombolysis),<sup>20,88</sup> alternative treatment strategies should be considered. For general adult patients in either group, ESC guidelines recommend surgical embolectomy (*class I, level C*) and suggest percutaneous catheter-directed therapies should be considered (*class IIa, level C*) if local institutional resources support either treatment. ECMO may also be considered in conjunction with either of those two treatments (*ESC class IIb, level C*). The level of evidence regarding these therapies in pregnancy-associated PE is low.

## CONCLUSION

Compared to age-matched controls, the risk of VTE is greatly increased during pregnancy and the early postpartum period. Clinical suspicion and diagnostic testing of VTE during these times should incorporate pregnancy-specific risk factors and epidemiologic considerations. CTPA and V/Q scintigraphy are both appropriate for PE imaging, but the choice may be influenced by specific elements of the patient's case. Most antepartum DVT and PE can be treated with LMWH alone, but treatment of severe DVT or PE may require thrombolysis or other advanced interventions, particularly during the first few days postpartum. Future research could improve care in this area by validating clinical decision tools for PE pretest probability (i.e., Wells and Geneva scores) and severity (i.e., PESI/sPESI scores; parameters for right ventricular dysfunction) in pregnancy and developing protocols for reperfusion of high-risk PE during the late antepartum and early postpartum periods.

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**Learning Objectives:**

After completing this activity, the reader should be able to (1) identify common risk factors for VTE in antepartum and postpartum women, (2) describe critical factors when obtaining diagnostic imaging for pregnancy-associated VTE, (3) identify critical elements for assessing PE severity, and (4) characterize treatment elements for mild and severe cases of pregnancy-associated VTE.

**Table 1:**

**Risk Factors Associated with Pregnancy-associated VTE**

Category	Risk Factor	Reference group	Antepartum risk		Postpartum risk		Source (convert to ref# before submission)
			Estimate	95% CI	Estimate	95% CI	
<b>Maternal Characteristics and Comorbidities</b>							
BMI & immobilization	BMI 25–29.9	BMI 18.5–24.9	1.4	0.98 – 2.0	1.3	0.9 – 1.8	20*
	BMI 30		1.4	1.0 – 2.0	1.7	1.1 – 2.7	22 <sup>†</sup>
	BMI 30–34.9		1.4	0.9 – 2.2	3.5	2.5 – 4.7	20*
	BMI 35		1	0.6 – 1.8	2.1	1.1 – 3.9	22 <sup>†</sup>
	BMI 25, no immobilization <sup>††</sup>		0.7	0.3 – 1.8	3.5	1.8 – 6.7	
	BMI <25, immobilization <sup>††</sup>		1.8	1.3 – 2.4	2.4	1.7 – 3.3	
	BMI 25, immobilization <sup>††</sup>		7.7	3.2 – 19.0	10.8	4.0 – 28.8	21 <sup>‡</sup>
	BMI 25, immobilization <sup>††</sup>		62.3	11.5 – 337	40.1	8.0 – 201.5	
Other	IBD	No IBD	2.1	1.7 – 2.7	2.6	1.8–3.7	25 <sup>§</sup>
	Preexisting diabetes	No diabetes	3.5	1.1 – 11.0	0.7	0.3 – 1.9	20*
	Varicose veins	No varicose veins	2.2	1.6 – 4.8	3.9	2.6 – 5.9	
<b>Antepartum Factors</b>							
Parity & Mode of Conception	Multiple gestation	Singleton	2.1	1.0 – 4.6	0.6	0.2 – 1.4	24
			0.8	0.3 – 2.7	0.9	0.4 – 2.1	20*
	Twins/spontaneous Singleton/ART Twins/ART	Singleton, spontaneous	2.8	1.9 – 4.2	1.3	0.6 – 2.6	22 <sup>†</sup>
			2.6	1.1 – 6.2	0.6	0.2 – 1.9	
			4.3	2.0 – 9.4	2.6	0.8 – 8.5	21 <sup>‡</sup>
Preeclampsia	No preeclampsia	6.6	2.1 – 21.0	0.6	0.1 – 7.6		
		0.8	0.4 – 1.6	3	2.0 – 4.4	24 <sup>¶</sup>	
				1.2	0.4 – 3.8	20*	
Preeclampsia & IUGR	Preeclampsia/no IUGR No preeclampsia/IUGR	No preeclampsia, no IUGR	1.2	0.4 – 3.6			22 <sup>†</sup>
			0.5	0.2 – 1.2	3.1	1.8 – 5.3	
			1.9	0.7 – 5.3	3.8	1.4 – 10.2	21 <sup>‡</sup>

Category	Risk Factor	Reference group	Antepartum risk		Postpartum risk		Source (convert to ref# before submission)
			Estimate	95% CI	Estimate	95% CI	
Other	Preeclampsia/IUGR		1	0.3 – 4.0	5.8	2.1 – 16.0	
	Gestational diabetes	No gestational diabetes	1.7	0.5 – 5.4	1.7	0.7 – 3.8	20 <sup>#</sup>
	Hyperemesis	No hyperemesis	1.2	0.4 – 3.9	4.5	0.9 – 23.1	21 <sup>‡</sup>
<b>Mode of Delivery &amp; Postpartum Complications</b>							
Delivery & Infection	Any cesarean delivery	Vaginal delivery			1.9	1.4 – 2.5	20 <sup>*</sup>
	Planned/elective cesarean				4.9	3.8 – 6.3	24 <sup>†</sup>
	Emergency/acute cesarean				2.1	1.4 – 3.1	22 <sup>‡</sup>
	Planned cesarean, no infection				1.4	1.0 – 1.9	23 <sup>**</sup>
	Emergency cesarean, no infection				3.3	2.3 – 4.0	22 <sup>‡</sup>
	Vaginal delivery, infection				2.1	1.6 – 2.6	23 <sup>**</sup>
	Any cesarean, infection				1.3	0.7 – 2.2	
Postpartum hemorrhage & surgery	Postpartum hemorrhage	No hemorrhage			2.7	1.8 – 4.1	21 <sup>‡</sup>
	Major postpartum bleeding				20.2	6.4 – 63.5	
	1000 mL/no surgery				6.2	2.4 – 16.2	
	< 1000 mL/surgery <sup>††</sup>				2.5	1.3 – 4.8	20 <sup>*</sup>
	1000 mL/surgery <sup>††</sup>				1.4	1.0 – 2.1	22 <sup>‡</sup>
Other	Preterm birth	No preterm birth			12	3.9 – 36.9	21 <sup>‡</sup>
					2.3	1.7 – 3.1	20 <sup>*</sup>

ART: assisted reproductive technology, BMI: body mass index, CI: confidence interval, IBD: inflammatory bowel disease, IUGR: intrauterine growth restriction.

<sup>\*</sup> Adjusted for age, parity, preexisting DM, IBD, varicose veins, acute systemic infection, and smoking status.

<sup>†</sup> Adjusted for age, calendar year, educational status, thrombophilia, anticoagulation treatment, medical diseases, assisted reproductive therapy, and parity.

<sup>‡</sup> Adjusted for age, parity, smoking status, weight gain, preeclampsia, BMI, immobilization, ART, and multiple pregnancy.

§ Meta-analysis estimate of 4 antepartum and 3 postpartum studies with varying approaches to confounder adjustment.

¶ Adjusted for age, parity, multiple pregnancy, smoking, and preeclampsia.

# Adjusted for age, parity, BMI, and smoking status.

\*\* DVT only. Adjusted for age, year of delivery, socioeconomic status, parity, hypertension, prior VTE, postpartum hemorrhage, preeclampsia, and mode of delivery.

†† Immobilization defined as strict bed rest for 1 week or more prior to delivery or to the diagnosis of VTE.

‡‡ Surgery postpartum included curettage for hemorrhage or remaining placental tissue; evacuation of hematoma or abscess; or reoperation for hemorrhage after cesarean.

**Table 2:**

**Thrombophilia Risk of Pregnancy-Associated VTE**

Thrombophilia	Population Prevalence	Prevalence in Pregnancy-Associated VTE	Odds Ratio for VTE	Confidence intervals	Sources
FVL heterozygous	2–7%	40%	6.4	3.9 – 10.6*	6, 34, 35
FVL homozygous	0.02–0.25%	2%	46.7	4.1 – 193.1*	6, 34
PGM heterozygous	1–2.3%	17%	4.3	2.0 – 8.8*	6, 34, 35
PGM homozygous	0.01%	0.5%	13.4	0 – 584.2*	6, 34
FVL/PGM compound heterozygous	0.01%	1–3%	26.6	1.1 – 147.1*	6, 34
Antithrombin deficiency	0.02%	1%	8.9	0.3 – 34.7*	6, 34
Protein C deficiency	0.2–0.5%	14%	7.7	0 – 48.1*	6, 34
Protein S deficiency	0.1–0.7%	3%	6.9	0.2 – 24.6*	3, 34, 35
Antiphospholipid syndrome	2–5%	Unknown	15.8	10–22.8	15, 35

FVL: Factor V Leiden. PGM: Prothrombin gene G20210A mutation. VTE: venous thromboembolism.

\* Bayesian credible interval rather than frequentist confidence interval.



**Table 3:**

Pharmacological Treatment Options for VTE in Pregnancy

Hemodynamically Stable PE or DVT		
Agent	SC doses	Frequency
Daltaparin	200 units/kg SC	Once Daily
	100 units/kg SC	Every 12 hours
Enoxaparin	1 mg/kg SC	Every 12 hours
Tinzaparin	175 units/kg SC	Once Daily
Hemodynamically unstable PE or limb-threatening DVT		
Agent	IV doses	FDA Approved for PE
Unfractionated heparin	80 mg/kg IV bolus, then 18 units/kg/hr infusion, adjust to goal aPTT	Yes
	Usual: 100 mg over 2 hours	Yes
	Accelerated: 0.6 mg/kg (max 50 mg) over 15 minutes	
Tenecteplase	30–50 mg bolus	No