JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 76, NO. 18, 2020

JACC FOCUS SEMINAR

Venous Thromboembolism Associated With Pregnancy

JACC Focus Seminar

Katherine M. Nichols, MD, Stanislav Henkin, MD, MPH, Mark A. Creager, MD

ABSTRACT

Venous thromboembolism (VTE), composed of pulmonary embolism and deep venous thrombosis, is a significant cause of maternal mortality in the developed world. Normal physiological changes of pregnancy increase coagulability, which is compounded by patient-inherited and acquired risk factors. Depending on these risks and peripartum stage, the benefits of thromboprophylaxis can outweigh potential side effects. Diagnosis requires cautious clinical acumen because many symptoms of normal pregnancy mimic those of VTE and algorithmic tools used in the nonpregnant population are not equally applicable. Choice of imaging technique must account for potential risk to the fetus and altered test accuracy (sensitivity and specificity) in the setting of pregnancy. When VTE is diagnosed, anticoagulation is the backbone of treatment, with more advanced therapies being options for those with right ventricular dysfunction or unstable hemodynamics. Overall, pregnancy-associated VTE is complex, and management decisions should be individualized and informed by patient preferences. (J Am Coll Cardiol 2020;76:2128–41) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Venous thromboembolism (VTE), specifically pulmonary embolism (PE) resulting from deep venous thrombosis (DVT), is the sixth leading cause of maternal death in the United States and the first in the United Kingdom and Ireland (1,2). Between 2011 and 2013, 9.2% of pregnancy-related deaths in the United States were due to PE (2,3). The risk of pregnancy-associated VTE is up to 6 times that of the general population, with an absolute risk up to 12.2 per 10,000, compared with 2 per 10,000 in nonpregnant women (4). Recognizing the magnitude and potential adverse consequences of this problem encountered in clinical practice, this review provides a contemporary perspective on risks, thromboprophylaxis, diagnosis, and treatment of VTE during pregnancy and the postpartum period.

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PATHOPHYSIOLOGY

Pregnancy is a prothrombotic state in ultimate preparation for bleeding prevention at the time of delivery. Coagulation factors II, VII, VIII, IX, X, XII, von Willebrand factor, and fibrin increase, protein S decreases, and there is increased resistance to activated protein C (5–10). Decreased venous flow velocity, venous distention, and obstruction of venous return by an enlarging uterus lead to stasis of blood flow. Taken together, these factors account for 6% to 11% of pregnancy-associated DVT (9,11–13). Vascular trauma during delivery, especially with the use of assist devices and Cesarean section, further heightens postpartum thrombotic risk.

From the Section of Cardiovascular Medicine, Heart and Vascular Center, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

Manuscript received April 3, 2020; revised manuscript received June 10, 2020, accepted June 16, 2020.

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2020.06.090

HIGHLIGHTS

- Prevention and management of venous thromboembolism (VTE) associated with pregnancy must consider outcomes of both mother and fetus.
- Treatment decisions should account for baseline and pregnancy-specific clinical factors and patient preferences.
- Randomized studies are necessary to identify safe, effective strategies for prevention and treatment of pregnancy-associated VTE.

RISK FACTORS

The most common risk factors for VTE in the general population remain present in pregnancy. In addition, there are pregnancy-specific risks (**Table 1**) (5,7,13–18).

Risk also increases with gestational age, peaking during the first 2 postpartum weeks. Compared with nonpregnant women, risk is more than 2-fold higher in the first and second trimesters, 9-fold higher in the third trimester, and 80-fold higher in the first 2 to 6 postpartum weeks (4,19,20). Induced abortion of pregnancy is associated with a 2-fold greater risk of VTE compared with that of the nonpregnant population (21,22).

Women with thrombophilia and those who undergo Cesarean section account for the majority of patients with postpartum VTE, ranging from 40% to 50% and 19% to 64%, respectively. Although Cesarean section deliveries carry a 4.9 times higher risk of VTE (95% confidence interval [CI]: 3.8 to 6.3) compared with vaginal deliveries, it is important to account for a degree of confounding because these patients often have more comorbidities. Preeclampsia increases DVT risk in the postpartum period (incidence rate ratio: 1.6; 95% CI: 1.01 to 2.53), but not in the antepartum period (incidence rate ratio: 1.03; 95% CI: 0.76 to 1.39) (23–25).

A prior history of VTE is a strong risk factor for pregnancy-associated VTE. The magnitude of risk depends on whether the prior VTE was unprovoked (3.6%), provoked (1.1%), or associated with exogenous hormone use (6.4%) (4,23). Given the potential implications of thrombophilia on length of treatment, antepartum care, and associated complications, guidelines, including those of the American College of Gynecology (ACOG), Society of Obstetricians and Gynecologists of Canada, and Royal College of Gynecologists, support consideration of testing all pregnant women with a history of VTE for antiphospholipid antibody syndrome and inherited thrombophilias, including Factor V Leiden (FVL) and prothrombin G20210A gene variant (PT G20210A), as well as antithrombin III, protein C, and protein S deficiencies (11,26,27).

Compared with other pregnant women, women with an inherited thrombophilia have a 15-fold higher risk (95% CI: 10.8 to 22.0) for a pregnancy-associated VTE, and absolute risk for DVT and PE of 146 per 10,000 and 43 per 10,000 pregnancies, respectively (4,28). Among women without a history of VTE, the magnitude of risk varies by specific thrombophilia and whether there is a family history of VTE. Family history independently increases risk of VTE up to 4-fold, even without the presence of a thrombophilia (29). Compared with pregnant women without thrombophilia, inherited thrombophilias associated with the highest risk of VTE in pregnancy are homozygous FVL (odds ratio [OR]: 34.4; 95% CI: 9.9 to 120.1), homozygous PT G20210A gene variant (OR: 26.4; 95% CI: 1.2 to 559.3), heterozygous FVL (OR: 8.3; 95% CI: 5.4 to 12.7), and heterozygous PT G20210A gene variant (OR: 6.8; 95% CI: 2.5 to 18.8) (**Figure 1**) (30). In compound heterozygotes, the individual probability of VTE is significantly higher than that of isolated mutations, ranging from 4.6% to 9.0% (OR: 47; 95% CI: 26 to 84; $p < 0.001$), independent of family history, and this increases with maternal age (31,32).

Endogenous anticoagulant deficiencies also increase risk of VTE, although less than inherited thrombophilias. Protein C, protein S, and antithrombin III deficiencies carry ORs of 4.8 (95% CI: 2.2 to 10.7), 3.2 (95% CI: 1.5 to 6.9), and 4.7 (95% CI: 1.30 to 17.0), respectively. The risk is further increased in those with a family history of VTE (33). Acquired thrombophilias, most notably antiphospholipid antibody syndrome, increase risk of pregnancy-associated VTE by 5% to 12% (34–36).

Assisted reproduction technologies (ART) involving ovarian stimulation increase the risk of VTE by 2- to 3-fold compared with the general pregnant population (37). This is attributed to supraphysiological estradiol levels, which lead to hemoconcentration and activation of coagulative and fibrinolytic systems (25,38). Thought possibly to be due to the draining of estrogen-containing ascitic

ABBREVIATIONS AND ACRONYMS

ACCP = American College of Chest Physicians

ACOG = American College of Gynecology

APLA = antiphospholipid antibody

ART = assisted reproductive technology

ASH = American Society of Hematology

CDT = catheter-directed thrombolysis

CT = computed tomography

CTPA = computed tomography pulmonary angiogram

CI = confidence interval

DOAC = direct oral anticoagulant

DVT = deep venous thrombus

ECMO = extracorporeal membrane oxygenation

FVL = Factor V Leiden

HIT = heparin-induced thrombocytopenia

IVC = inferior vena cava

LMWH = low-molecular-weight heparin

MRA = magnetic resonance angiography

OHSS = ovarian hyperstimulation syndrome

OR = odds ratio

PE = pulmonary embolism

PT = prothrombin

RV = right ventricle

UFH = unfractionated heparin

VTE = venous thromboembolism

fluid through the lymphatic system into the thoracic duct and subsequently the left subclavian vein, ART-related VTEs are more likely to occur in the upper extremities (37,38). The majority of ART-associated VTEs occur during the first trimester, when there is a 5- to 10-fold increased risk compared with other pregnant women. There is no significant difference in the second and third trimester (39). The presence of multiple gestations does not increase the first trimester VTE risk when compared with the non-VTE pregnant population, but does increase that of the entire antepartum period by 2.1- to 2.6-fold (39). In ART that does not result in conception, there is no increased risk (37).

In up to 8% of women who undergo ART, the stimulatory response is exaggerated, resulting in ovarian hyperstimulation syndrome (OHSS) (39). In these individuals, VTE risk is up to 100-fold higher in the first trimester (25,37), and, when diagnosed, it occurs earlier (a mean 18 days with OHSS vs. 57 days without OHSS) (37). In patients with a prior history of VTE or thrombophilia, data regarding increased risk of VTE during ART is lacking and degree of increased risk, if any, is unclear.

PROPHYLAXIS

Despite the established risk of VTE during pregnancy, thromboprophylaxis is not beneficial for all women. Prophylaxis carries risk of maternal bleeding complications of up to 2% as well as heparin-associated osteoporosis and heparin-induced thrombocytopenia (HIT) (2,40–43). Warfarin crosses the placenta, and is associated with increased rates of miscarriage, congenital anomalies, fetal bleeding, and long-term neurological consequences, making it a Food and Drug Administration category D drug (44–46). Fondaparinux and some direct oral anticoagulants (DOACs), including apixaban and rivaroxaban, also cross the placenta, but the clinical effect on fetal outcome is not well established (47–49). Thus, DOACs are not recommended in pregnancy (50,51). Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have the most favorable safety profile, but many patients cite injections and daily to twice a day dosing frequencies as uncomfortable, burdensome, and a source of additional cost. The potential for unpredictable onset of labor, epidural catheter placement, and need for emergent Cesarean section complicates the use of the longer-acting LMWH. For these reasons, the threshold for prophylactic therapy during pregnancy is typically higher than that in the postpartum period where the indicated duration is shorter and there is the additional option to use warfarin. Taking these factors into consideration, the indication for thromboprophylactic therapy should be based on a patient's unique clinical risk factors and gestational period.

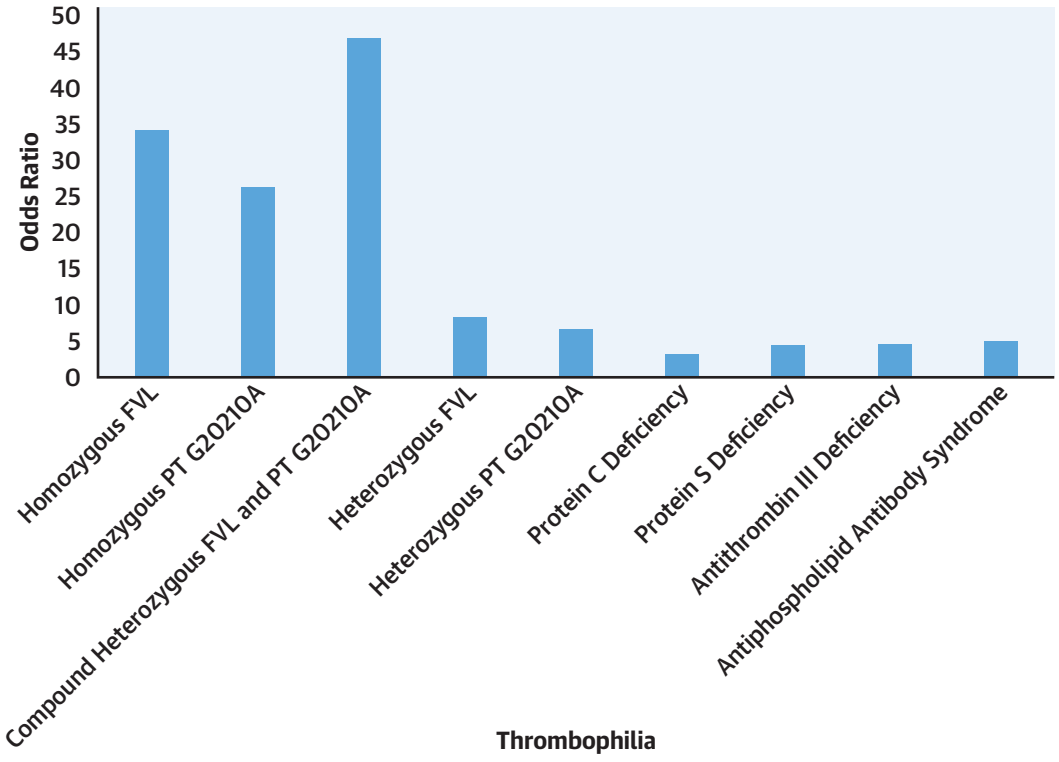
TABLE 1 VTE Risk Factors in Pregnancy

Personal history of VTE
Thrombophilia
Age >35 yrs
Body mass index >30 kg/m^2
Immobility
Nulliparity
Multiple gestation
Gestational diabetes
Pre(eclampsia)
Cesarean section
Antepartum hemorrhage
Postpartum infection
Hypertension
Diabetes
Smoking
Sickle cell disease
Systemic lupus erythematosus

VTE = venous thromboembolism.

There are no studies in pregnant women directly comparing prophylactic LMWH versus UFH; however, in the nonpregnant population, LMWH is equal in safety and efficacy to UFH (52,53). LMWH has a more predictable response and lower incidence of osteoporosis and HIT, although UFH may be preferred in patients with renal dysfunction (glomerular filtration rate <30 ml/min) or in whom rapid drug reversal may be required, such as prior to an operation or delivery (42,54–56). Prophylactic UFH is administered every 12 h subcutaneously in pregnancy. Although 5,000 U is the standard prophylactic dose, there is some evidence that this is inadequate as pregnancy progresses, and many choose to increase the dose by trimester (5,000 to 7,500 U in the first, 7,500 to 10,000 U in the second, and 10,000 U in the third) (57). For prophylactic LMWH, an evidenced-based consensus regarding optimal dosing strategy is lacking with option of prophylactic (e.g., enoxaparin 40 mg subcutaneous daily), weight adjusted (0.5 mg/kg subcutaneously twice a day), or intermediate (defined as higher than prophylactic but less than therapeutic) (**Table 2**). One randomized trial of prophylactic dose versus weight-based enoxaparin in post-Cesarean section obese patients (body mass index ≥35 kg/m^2) did not show significant differences in the rate of VTE events or major bleeding (58). Other studies comparing dosing strategies are non-randomized and showed no difference in efficacy or safety between different doses (59–61). Consequently,

FIGURE 1 Venous Thromboembolism Risk by Thrombophilia in Pregnancy



Compared with pregnant women without thrombophilia, women with thrombophilia, particularly homozygous mutations of Factor V Leiden (FVL) or prothrombin G20210A gene variant (PT G20210A) and compound heterozygotes, are at increased risk for venous thromboembolism during pregnancy.

given the increased cost of greater than prophylactic dosing and anesthesia guidelines that recommend at least 24 h between the last greater than prophylactic dose of LMWH and epidural catheter placement (vs. 12 h for a prophylactic dose), a prophylactic LMWH dose is recommended by the American Society of Hematology (ASH) rather than other doses (62). Alternatively, the American College of Chest Physicians (ACCP) and ACOG recommendations support the use of both prophylactic and intermediate dosing (26,63). Currently, a randomized controlled study comparing prophylactic and weight-adjusted LMWH in patients with prior history of VTE is recruiting (NCT01828697).

As time of expected delivery nears, allowing for spontaneous delivery with discontinuation of prophylactic LMWH at the time of labor onset is advantageous compared with a scheduled delivery with discontinuation 12 to 24 h prior (12 h for prophylactic dose; 24 h for higher dose). Spontaneous labors may be associated with lower maternal and neonatal complications and need for medical intervention (64,65). Many providers choose to transition LMWH to twice-daily UFH at 36 to 37 weeks' gestation to improve access to neuraxial anesthesia (26,66).

The majority of bleeding during delivery is secondary to placental separation. Bleeding is controlled by myometrial contractions, which occlude uterine blood vessels, rather than by the coagulant factors targeted by anticoagulant therapy. Alternatively, bleeding from soft tissue tears and trauma during delivery is sensitive to anticoagulant therapy (67). Prophylactic LMWH can be resumed 4 to 12 h after delivery, and 4 h after epidural catheter removal (68). Postpartum, the benefit of prophylactic therapy extends to 6 weeks, after which the absolute risk decreases to <1/10,000, making it acceptable to discontinue (69).

In pregnant women with 0 or 1 clinical risk factor (**Table 1**), not including prior VTE or history of thrombophilia, there is no indication for prophylaxis in the antepartum or postpartum periods. The

TABLE 2 Prophylactic and Therapeutic Anticoagulant Dosing Strategies

Drug	Prophylactic	Intermediate	Weight Adjusted	Weight Adjusted or Full Tx
LMWH				
Enoxaparin	40 mg SC qd	40 mg SC BID	0.5 mg/kg BID	1 mg/kg BID
Dalteparin	5,000 U SC qd	5,000 U SC BID or 10,000 U daily		200 U/kg qd or 100 U/kg q12h
Tinzaparin	4,500 U SC qd	10,000 U daily	75 U/kg daily	175 U/kg daily
Nadroparin	2,850 U SC qd			86 U/kg BID or 171 U/kg qd
UFH	5,000–10,000 U SC BID	5,000–7,500 U SC TID		17,500 U BID for goal anti-Xa 0.3–0.7 IU/ml
IV UFH				80 U/kg bolus then 18U/kg/h; titrate for anti-Xa 0.3–0.7 IU/ml
Fondaparinux	2.5 mg SC qd			5 mg SC daily (weight <50 kg), 7.5 mg (50–100 kg), 10 mg (>100 kg)

BID = twice daily; TID = three times daily; qd = every day; q12h = every 12 h; SC = subcutaneous; UFH = unfractionated heparin.

majority of individual risk factors have a low absolute risk of <1%. The combined effects of multiple risk factors, whether additive or multiplicative and to what extent, are unknown and available data is primarily from underpowered and inadequately designed studies. Several prediction models have been developed to aid risk assessment for postpartum VTE; however, these have not been fully assessed for prospective use (39,70–74). Overall, the potential harm and burden of prophylactic therapy for low-risk patients in the antepartum and postpartum periods outweigh the net health benefit.

Although there is a clear association between gestational period and VTE, there is no evidence to support an indication for prophylaxis by gestational age in most women. However, for specific patient subsets, which include those with a history of prior VTE or thrombophilia, the change in risk profile over the course of pregnancy is more relevant and influences the indication for prophylactic treatment. Gestational period also influences selection of anticoagulant; LMWH is the preferred choice in the antepartum period, and LMWH or vitamin K antagonist with international normalized ratio range of 2.0 to 3.0 can be used postpartum; however, this range is based on opinion rather than randomized trial data (63). DOACs are not recommended in lactating women.

Among women with a history of VTE, prophylactic therapy significantly reduces the incidence of recurrent VTE in the antepartum and postpartum periods, with no significant increase in major hemorrhage, osteopenia, osteoporotic fracture, or HIT. Risk of VTE is decreased by ~75%, to an incidence rate of 0.9% to 2.8% antepartum and 1.7% postpartum. Studies have suggested that women with a prior VTE associated with pregnancy or oral contraceptive use are more likely to have a recurrent VTE in pregnancy than those with an unprovoked or non-hormone-associated prior VTE (75–77). Additional data on risk by type of prior VTE is limited and guideline recommendations extract data from orthopedic studies of patients who carry similar risks of VTE (78). Thus, several guidelines state that prophylactic anticoagulation is beneficial in antepartum women with either unprovoked or hormone-associated VTE and postpartum in women with any prior VTE, regardless of etiology (79,80).

The most significant reduction in VTE risk with prophylaxis occurs in patients with both a family history of VTE and either homozygous FVL or homozygous PT 20210A gene mutation. In these patients, 47 per 1,000 fewer experienced VTE in both the antepartum and postpartum periods. For those without a positive family history of VTE or with heterozygote variants, a reduction of 13 per 1,000, and 10 per 1,000, respectively, was observed. In patients with a positive family history of VTE and antithrombin III, protein C, or protein S deficiency, prophylaxis resulted in 13 fewer patients per 1,000 with VTEs (63).

In thrombophilic patients with history of VTE, thromboprophylaxis is beneficial both antepartum and postpartum. In thrombophilic patients without a history of VTE, recommendations for antepartum and post-partum thromboprophylaxis are dependent on the type of thrombophilia and family history of VTE. Relevant guidelines for prophylaxis in the antepartum and postpartum periods have been developed by several professional societies, including ASH, ACOG, and ACCP. Recommendations are outlined in **Table 3**.

In patients with antiphospholipid antibody syndrome and a history of recurrent pregnancy loss, combined prophylactic low-dose aspirin and heparin may reduce miscarriage by up to 50% and should be considered for use in the prenatal period, and

continued to 6 weeks postpartum (36). For all patients with thrombophilia in whom thromboprophylaxis is indicated, treatment should begin as early as possible in the first trimester and continue up to 6 weeks postpartum. It is important to note that patients with protein C or protein S deficiency who are treated with warfarin are at risk for skin necrosis, although this complication is uncommon (81-83).

Overall, studies regarding thromboprophylaxis for ART patients vary greatly in the availability of data regarding use, type, and dosing of medication, leading to uncertainty of the ideal treatment strategy. As such, thromboprophylaxis is not routinely recommended for these patients. A study comparing the incidence of VTE in ART patients treated with LMWH ± aspirin versus no anticoagulant or antiplatelet agent showed a trend of increased VTE in the nontreatment arm, but this was not statistically significant (25). Additionally, prophylactic aspirin or LMWH in ART patients has not been shown to improve the rate of successful pregnancy (84-87). However, in patients with OHSS, where risk of VTE in the first trimester is increased by 100-fold, prophylaxis with LMWH is indicated for the first trimester only (25,37). Although LMWH is the preferred medication, there is no evidence-based optimal treatment strategy reported. Nonetheless, Lindqvist et al. (39,88) recommend a dose equivalent of at least 5,000 U dalteparin once daily.

For patients with a personal history of VTE or thrombophilia, the degree of additional risk conveyed by the use of ART is unclear. Limited available data has shown that neither FVL nor PT G20210A gene mutation alter thrombotic risk among women receiving ART (89). Thromboprophylactic strategy in these patients should, therefore, be the same as non-ART patients, dictated by their underlying VTE and thrombophilia history (37,39).

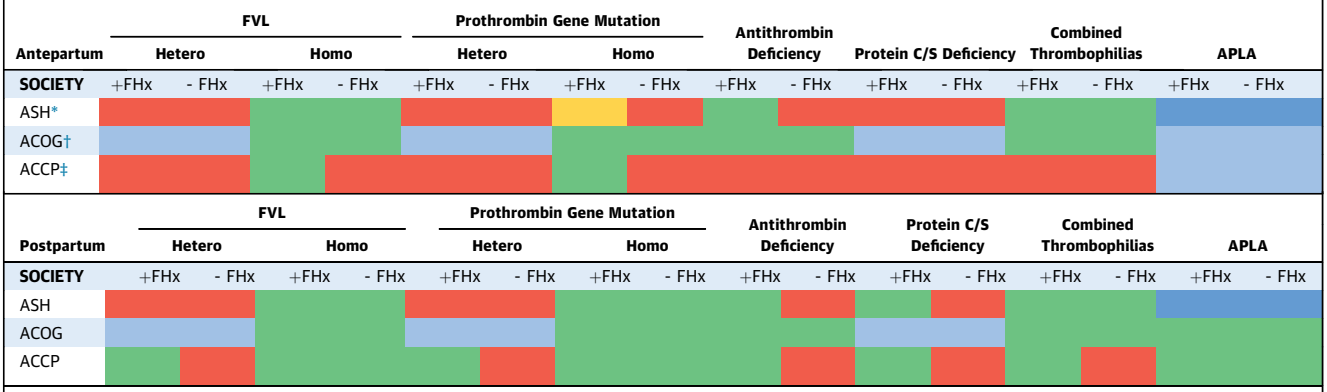
DIAGNOSIS

Clinicians must balance the potential harms of diagnostic testing with the need to establish the diagnosis of VTE and promptly initiate therapy. Many typical symptoms of pregnancy, such as leg swelling and shortness of breath, mimic those of VTE. Risk prediction models and algorithms used in the nonpregnant population, such as the Wells criteria, Modified Geneva score, and SimpliRED D-dimer, have not been validated in pregnant women (90-93). Traditional laboratory testing of D-dimer levels has been largely unreliable in pregnancy because they continuously increase during normal pregnancy and are often above "rule out" limits in the second and third trimester. This is due to increased thrombin activity and fibrinolysis, as well as events such as placental abruption and preeclampsia, decreasing the test specificity (10,94-96). However, a recent study examined the use of D-dimer in combination with a developed algorithm of taking clinical signs of DVT, hemoptysis, and PE as the most likely diagnosis into account. PE was safely ruled out in 498 women with suspected PE, sparing 32% to 65% of them from a computed tomography pulmonary angiogram (CTPA), thus reducing radiation to the fetus (97).

For diagnosis of DVT in the symptomatic, pregnant woman, venous duplex ultrasonography is the standard of care. However, unlike in the general population where 80% of DVTs are located in the calf, the majority of DVTs in pregnancy are located proximally, affecting the iliofemoral veins (62%), with only 6% in the veins of the calves (98,99). The deeper, intrapelvic location of the iliofemoral veins in combination with the gravid uterus makes imaging during the compression maneuver of venous duplex ultrasonography challenging, and theoretically decreases the sensitivity and specificity of the test. To improve diagnostic accuracy, a strategy of serial venous ultrasonography has been evaluated. In a study of symptomatic, pregnant women, daily serial venous duplex ultrasonography was performed over 7 consecutive days (99). Of those women confirmed to have DVT, all were diagnosed on the initial venous duplex ultrasound examination, suggesting that even in pregnancy, duplex ultrasound has appropriate sensitivity. Where available, magnetic resonance venography is another validated imaging option and detects twice as many pelvic abdominal DVTs when compared with ultrasound (98.5% vs. 42.0%) (100). Limitations of this imaging modality include higher cost, accessibility, duration of test, and time to result.

As in the general population, the diagnosis of PE is dependent on thoracic imaging, including CTPA, pulmonary scintigraphy (V/Q scan), and chest magnetic resonance angiography (MRA). Complicating the choice of imaging modality are maternal and fetal exposure to radiation and imaging contrast, as well as the availability and diagnostic sensitivity and specificity of each test. CTPA and V/Q scanning both require radiation, which has been associated with increased maternal risk of cancer, particularly of the breast, and depending on gestational age and dose, increases the fetal risk of growth restriction, microcephaly, and intellectual disability (101). Maternal radiation exposure is higher with CTPA than with V/Q scanning, with average effective and breast-absorbed doses of 21 mSv and 44 mGy, compared with 1.04 mSv and 0.28 mGy with VQ scanning (102). However,

TABLE 3 Society Guideline Recommendations for VTE Prophylaxis in the Antepartum and Postpartum Periods



Dark blue = no comment; FHx = family history; green = yes; yellow = indeterminate; light blue = prophylaxis or close monitoring of patient; red = no. *American Society of Hematology; †American College of Obstetricians and Gynecologists; ‡American College of Chest Physicians.

FHx = family history of VTE; VTE = venous thromboembolism.

recent data have shown that modern imaging techniques have reduced breast radiation exposure to as low as 3 to 4 mGy and has a negligible impact on maternal cancer risk (1,103-105). Comparatively, fetal radiation doses are lower with CTPA at 0.01 to 0.66 mGy versus 0.1 to 0.5 mGy with V/Q scanning, and doses in both tests are below the suggested accepted maximal cumulative threshold of 50 mGy (101,106). Additionally, use of V/Q scans is limited by availability and indeterminate results. False-negative rates for V/Q scanning and CTPA in pregnancy are similar at 0.5% (95% CI: 0.2 to 1.3) and 0.4% (95% CI: 0.2 to 1.3), respectively. A meta-analysis evaluating the sensitivity of both tests in pregnancy showed a median sensitivity of 83% for CTPA and 100% for V/Q scanning, although both had ranges of 0 to 100% and there was no direct comparison with statistical testing (107). This is notably higher than the sensitivity of V/Q scanning reported in the general population, which is 77.4% (95% CI: 69.7 to 85.0) for a high probability scan (108). MRA has the advantage of being radiation free; however, there is limited data available on technique, and fetal gadolinium exposure has been associated with fetal skeletal and visceral developmental abnormalities in animals (107). There is also theoretical concern for potential fetal harm from the effects of magnetism and radiofrequency pulses, although this has never been proven (109). In light of unknown safety data with MRA, equal fetal radiation exposure with CTPA and V/Q scans, and greater access and faster results with CTPA, CTPA is the most advantageous imaging method.

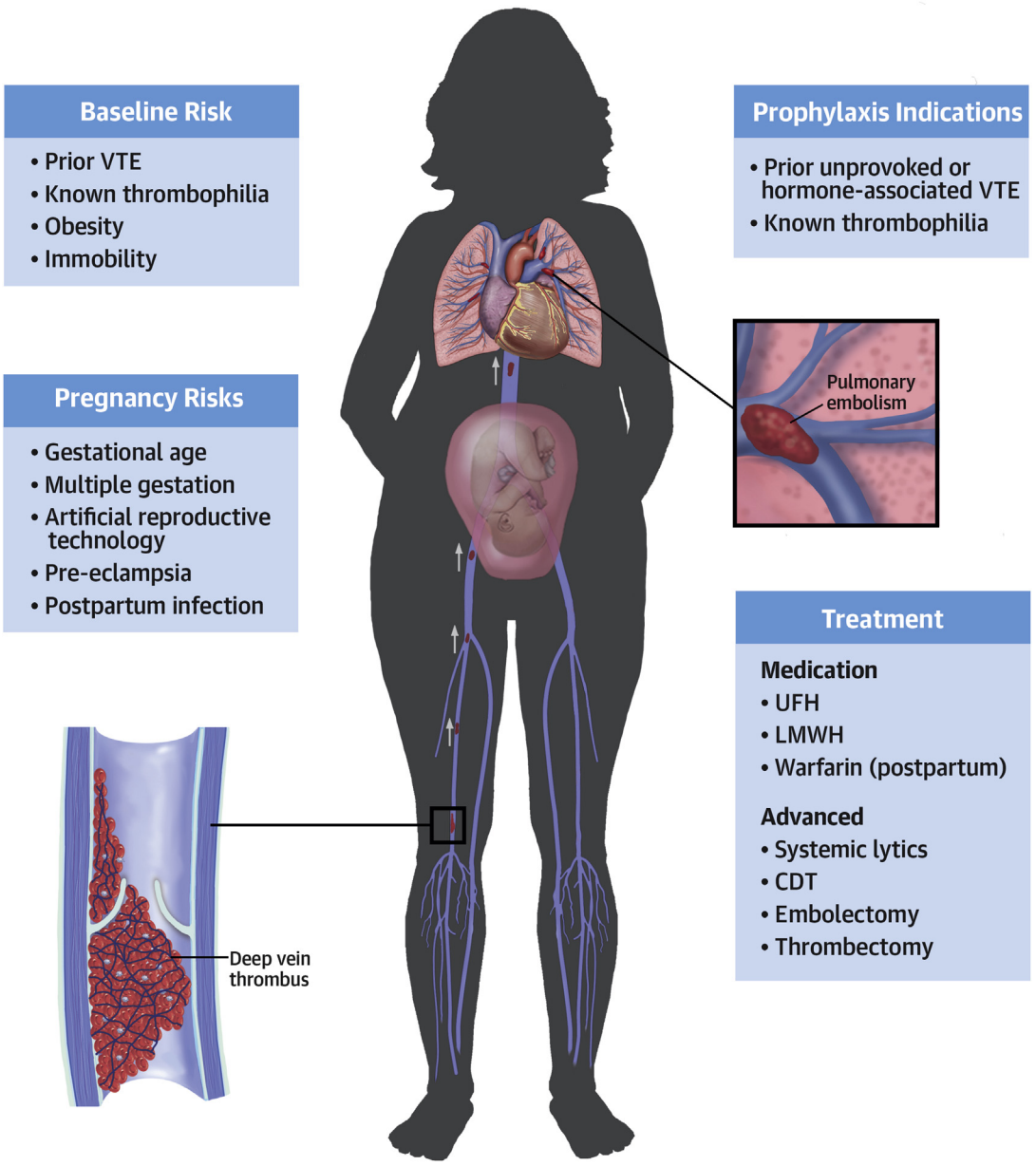
TREATMENT

Essentially all pregnant patients diagnosed with VTE should be treated with systemic anticoagulant therapy. For patients who do not tolerate or who are not candidates for anticoagulation, inferior vena cava (IVC) filter may be an option.

ANTICOAGULANT THERAPY. LMWH and UFH are the most evidence-supported anticoagulant agents for treatment of VTE in pregnancy and they reduce VTE mortality and recurrence (52,110,111). In the nonpregnant population, when compared with UFH treatment, therapeutic LMWH has comparable efficacy on reducing thromboembolic recurrence, equal risk of all-cause bleeding, and greater reduction of thrombotic complications, major hemorrhage, and death; because it does not cross the placenta, LMWH carries no risk of fetal hemorrhage (52,53,112,113). Given these features, LMWH is the preferred treatment for therapeutic anticoagulation during pregnancy in patients with a glomerular filtration rate > 30 ml/min (42,55,56,114). In those with glomerular filtration rate < 30 ml/min, UFH should be used. In patients with HIT, guidelines from ACOG, ACCP, and ASH recommend danaparoid because it has not been shown to cross the placenta. In the United States where danaparoid is not available, fondaparinux is an alternative option with the understanding that evidence of its transplacental passage and the potential for fetal harm is not known (50).

Therapeutic UFH and LMWH doses for use in pregnancy are shown in **Table 2**. UFH is typically started with a continuous intravenous infusion and

CENTRAL ILLUSTRATION **Aspects of Care of VTE in the Pregnant Patient**



Nichols, K.M. et al. J Am Coll Cardiol. 2020;76(18):2128–41.

In managing pregnant patients, indication for prophylaxis is determined by assessment of baseline clinical and pregnancy-specific risk factors. Upon diagnosis of a VTE, choice of treatment strategy must take both maternal and fetal health into account. CDT = catheter-directed thrombolysis; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism.

transitioned to dose-adjusted twice-daily subcutaneous UFH, or begun immediately as dose-adjusted twice-daily UFH to obtain partial thromboplastin time or anti-Xa level within therapeutic ranges. Data supporting an ideal LMWH dosing strategy in pregnant patients is limited, and most recommendations stem from the nonpregnant population, despite concern about the differing pharmacokinetics of pregnancy. In a single study of daily versus twice a day LMWH dosing in nonpregnant patients with VTE,

there was no difference in the risk of recurrent VTE or bleeding (115). Studies of pregnant patients receiving single versus twice-daily dosing did not demonstrate a difference in bleeding rates, but were small and observational (116,117). Although there is evidence that up to 74% to 91% of patients on LMWH have subtherapeutic trough anti-Xa levels, and that a 10% to 20% increased dose is often required to achieve goal levels, routine monitoring of anti-Xa levels has not been shown to have a clear benefit in observational studies (8,57,114,118,119). Additionally, a large ($n > 35,000$) single-center case series examined the use of anti-Xa level adjusted LMWH dosing (for a goal peak plasma anti-Xa activity of 0.5 to 1.0 IU/ml) versus weight-adjusted LMWH (tinzaparin 175 IU/kg once daily) dosing. No statistically significant difference was found in average LMWH dose, risk of maternal blood loss, or recurrent thromboembolic events between the 2 groups (119). Nonetheless, monitoring of anti-Xa levels might be considered in patients with renal insufficiency or obesity to ensure these are in the therapeutic range (120,121). In these cases, peak anti-Xa levels are obtained 4 to 6 h after dosing, and titration of dose to achieve a level of 0.6 to 1.2 U/ml. Anti-Xa levels are checked every 4 to 6 weeks or after a dose adjustment (26).

As time of delivery approaches, providers may elect to switch from daily to twice-daily LMWH dosing, or to UFH to allow for shorter half-life, preventing delivery under full anticoagulation and enabling access to neuraxial anesthesia (18). Once the pregnant woman is admitted for delivery, LMWH can be transitioned to a continuous heparin infusion ≥36 h prior to delivery and stopped 4 to 6 h before delivery to allow for normalization of partial thromboplastin time or the anti-Xa level. If a patient remains on LMWH, it should be discontinued 24 h prior to a scheduled delivery (18). In a single-center retrospective study, women were switched from daily LMWH to twice-daily weight-adjusted dosing at 37 weeks (59). In those whose anticoagulation was discontinued at the start of spontaneous labor, there was a trend (OR: 1.9; 95% CI: 0.6 to 5.8; $p = 0.29$) toward increased risk of postpartum hemorrhage (>500 ml) in comparison with those with scheduled delivery and anticoagulation discontinued 24 h prior (59). For vaginal deliveries, women on LMWH had a 1.9 times higher risk (95% CI: 1.1 to 3.5; $p = 0.029$) of postpartum hemorrhage (>500 ml) compared with those not on LMWH, but there was no significant difference for severe postpartum hemorrhage (>1,000 ml). There was no significant difference in risk of postpartum hemorrhage in patients undergoing Cesarean section (OR: 2.9; 95% CI: 0.5 to 19.4; $p = 0.26$).

Following delivery, therapeutic LMWH or UFH can be restarted 24 h after epidural catheter removal, 6 to 12 h after a vaginal delivery, or 12 to 24 h after Cesarean section, if there are no bleeding concerns (113). Because the risk of VTE peaks at 2 weeks postpartum, therapeutic anticoagulation should be continued for at least 6 weeks postpartum, and, ideally, 3 months. Length of therapy is patient centered and depends on the underlying cause of VTE (4,113).

In the postpartum period, breast-feeding mothers can either continue the antepartum anticoagulant, such as LMWH or UFH, or switch to warfarin or fondaparinux. Although there is limited data on the safety and effect on neonatal bleeding of different treatments, these anticoagulants have been demonstrated to be safe in observational studies, with undetectable or very low amounts of drug being detected in breast milk, likely due to molecular size, charge, lipophilic profile, and oral bioavailability (122–124). Use of DOACs is not recommended because they have not been extensively studied in pregnancy and safety data is not established (125,126).

IVC FILTER. In patients who have recurrent VTE while on full-dose medical therapy or have a contraindication to systemic anticoagulation, placement of an IVC filter is an option. IVC filter placement is primarily performed under fluoroscopy, and after fluoroscopy, the amount of associated fetal radiation exposure has not been deemed significant by the International Commission of Radiological Protection (127). There are no current reports on the use of intravascular ultrasound guidance in the pregnant population, but it may be an option to eliminate radiation exposure (128). Filters may be placed via jugular or femoral access with no difference in safety, insertion difficulty, or impact on the remainder of the pregnancy (129).

In a systematic review, IVC filters did not appear to significantly increase fetal morbidity or mortality, but were associated with a maternal morbidity rate of 8.8% to 11.3%, similar to complication rates in the nonpregnant population (129,130). Reported complications directly related to filter placement included: threatened preterm labor immediately after filter placement that resolved with tocolysis; retroperitoneal hematoma; and transient leg swelling. Some studies have reported filter complications of migration, tilt, fracture, and retrieval, particularly in relation to venous dilation with labor, contractions,

and changes in IVC diameter and displacement before and after delivery (18,129,131–136). Given the potential for these changes, Cesarean delivery may be preferable in patients with an IVC filter. It is also important to note the lack of data regarding long-term safety of IVC filter placement in a generally young patient population. Accordingly, placement of IVC filters should be reserved for patients in whom there is a contraindication to anticoagulant therapy.

ADVANCED THERAPIES

Advanced therapies, such as catheter-directed thrombolysis (CDT) or thrombectomy, may be considered in patients with limb-threatening proximal DVT, manifest as phlegmasia alba dolens or phlegmasia cerulean dolens. Life-threatening massive PE (sustained systolic blood pressure <90 mm Hg for at least 15 min or requiring inotropic support) often requires advanced therapies, including systemic thrombolysis, CDT, surgical thrombectomy, catheter-based embolectomy, or extracorporeal membrane oxygenation (ECMO) (137). Use of some advanced therapies may also be considered in patients with submassive PE (without systemic hypotension, but with either right ventricle [RV] dysfunction or myocardial necrosis) (137). Specific treatment modalities are discussed as follows.

CDT. CDT is a nonsurgical, percutaneous treatment option for targeted lytic delivery directly into the compromised vessel, without or with ultrasound-assistance catheters (EKOS, Boston Scientific Company, Marlborough, Massachusetts). In a study of 11 pregnant women with DVT treated with pharmacomechanical CDT, 9 had >90% clot lysis and none had a major complication or post-thrombotic syndrome at the time of treatment or at a 20-month median follow-up (138). Although most women chose to abort pregnancies after treatment, 3 of the 11 had successful, full-term pregnancies. In another study of 11 women with iliofemoral DVT treated with CDT and/or pharmacomechanical thrombolysis, all had near or complete venous patency following treatment, delivering healthy, full-term infants (139). Radiation doses vary, but a small case series did show fetal exposure levels to be above the maximal accepted limit for major organ malformation (139,140). Accordingly, CDT is not recommended for routine use, should be avoided in the first trimester, and is reserved for threatened life or limb or failure of medical therapy in the second and third trimesters (5,18,138,139). In patients with PE, studies have shown that CDT decreases RV/left ventricle ratio faster and more significantly compared with anticoagulation alone. Data for long-term benefits of CDT are lacking because observational studies have shown no benefit in long-term RV function or mortality; additionally, CDT is associated with a higher risk of bleeding (141–143). Moreover, none of the studies included pregnant women. In pregnant women with PE, 3 case series describe the use of CDT, each demonstrating successful use of CDT ± fragmentation therapies in hemodynamically unstable patients (15,144,145). Notably, CDT requires the use of fluoroscopy.

SYSTEMIC THROMBOLYSIS. Systemic thrombolysis consists of administration of an intravenous lytic, such as alteplase and tenecteplase, to hydrolyze fibrin molecules (146). These agents can more rapidly improve patient's hemodynamics, symptoms, and probability of survival while also reducing RV damage and PE recurrence with no difference by thrombolytic regimen (147). As described in a systemic review and meta-analysis, however, these overall observed benefits are accompanied by a significantly increased risk of major bleeding (OR: 2.91; 95% CI: 1.95 to 4.36) and intracranial or fatal hemorrhage (OR: 3.18; 95% CI: 1.25 to 8.11) (137,147).

In pregnancy, alteplase does not cross the placenta in amounts significant enough to cause fetal coagulopathy (148,149). A systematic review of studies of antepartum and postpartum women treated with systemic thrombolysis reported maternal survival to be up to 94% (95% CI: 86% to 98%) (150), but a 28.4% (95% CI: 19% to 40%) risk of major maternal bleeding, mostly occurring after delivery due to vaginal hemorrhage or post-Cesarean section abdominal bleeding (147,150). Fetal or neonatal death just before, during, or shortly after systemic lytic administration is reported to be 12%, whereas 35.1% of pregnant women receiving thrombolytic therapy had a pre-term delivery (150). The timing of these events suggest that the presence of fetal demise may be related to the hemodynamic changes induced by the PE versus the lytic medication itself.

OTHER ADVANCED THERAPIES. Percutaneous thrombectomy (thrombus aspiration, fragmentation of thrombus by catheter, or rheolytic thrombectomy), surgical embolectomy, and ECMO are additional, invasive options for patients with submassive or massive PE who do not improve with thrombolytic therapy or have a contraindication. In a report of 7 pregnant women treated with percutaneous thrombectomy, maternal survival was 86.1% (95% CI: 71% to 95%), major bleeding risk was 20% (95% CI: 1% to 72%), and risk of fetal death was 25% (95% CI: 1% to 81%) (150). Surgical embolectomy can warrant good results but is dependent on local

expertise and availability of cardiopulmonary bypass. In a series of 8 antepartum cases, there was 100% maternal survival, and 3 fetal deaths (148). In another report of 21 antepartum and postpartum patients, 93.8% had significant hemodynamic improvement. Maternal survival was 86.1% (31 of 36) with 2 deaths occurring after surgery and 3 resulting from cerebral hypoxia related to the acute event (150). Major bleeding episodes occurred in 20% and fetal loss in 20%. Data supporting the use of ECMO in pregnancy is primarily limited to use in acute respiratory distress syndrome with only case reports in massive PE, which all showed high maternal survival rates without major bleeding, but a meaningful conclusion is limited by the low number of cases (150–152). ECMO is also largely dependent on trained staff and institutions.

CONCLUSIONS

Pregnancy-associated VTE is a leading contributor to maternal morbidity and mortality (**Central Illustration**). Normal pathophysiological changes during pregnancy create a prothrombotic milieu, expanding baseline risk, and require risk stratification to determine those who will derive the greatest benefit from thromboprophylaxis. For patients presenting with clinical features of VTE, diagnostic strategies must take both fetal and maternal factors into consideration, and providers should be aware of the potential for altered test interpretation (in regard to sensitivity/specificity) compared with the nonpregnant population. Once VTE is diagnosed in the pregnant woman, the choice of anticoagulant for treatment must take into account gestational age and risk of maternal and fetal complication peri-delivery. Various advanced, invasive therapies can be life-saving for the woman, but risk of fetal morbidity and mortality is notable. VTE presents unique challenges in the pregnant patient and requires providers to use a multi-faceted approach, combining guideline recommendations with patient-centered, shared decision making to provide the highest level of comprehensive care.

ADDRESS FOR CORRESPONDENCE: Dr. Mark. A. Creager, Director, Heart and Vascular Center, Dartmouth-Hitchcock Medical Center, Anna G. Huber Professor of Medicine, Geisel School of Medicine at Dartmouth, 1 Medical Center Drive, Lebanon, New Hampshire 03756. E-mail: mark.a.creager@hitchcock.org. Twitter: @DrMarkCreager.

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KEY WORDS anticoagulation, deep vein thrombosis, pulmonary embolism, thrombolysis