ASH CLINICAL PRACTICE GUIDELINES
VENOUS THROMBOEMBOLISM (VTE)

POCKET GUIDE

Venous Thromboembolism (VTE) in the Context of Pregnancy

A POCKET GUIDE FOR THE CLINICIAN

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The recommendations in this guide are based on the American Society of Hematology 2018 Guidelines for Management of Venous Thromboembolism: Venous Thromboembolism in the Context of Pregnancy

Context

Pregnancy-associated venous thromboembolism (VTE) is a leading cause of maternal morbidity and mortality. The information in this pocket guide is intended to support patients, clinicians, and other health care professionals in their decisions about the diagnosis, prevention, and treatment of pregnancy-associated VTE as well as maternal and fetal well-being. This pocket-guide contains information specifically pertaining to the treatment of acute VTE and superficial vein thrombosis, management of anticoagulants around the time of delivery, anticoagulation use in breastfeeding women, prevention of VTE, and diagnosis of VTE.

Prevention of VTE

Pregnancy and the postpartum period have an increased risk of VTE due to a combination of increased levels of some clotting proteins, decreased levels of some natural blood thinning proteins, and slowed blood flow in the veins due to pressure on those vessels. Patients with a personal or family history of blood clots, blood clotting disorders, and other risk factors for clotting are at higher risk of developing pregnancy-associated VTE. The use of VTE prophylaxis prevents complications secondary to blood clots, reduces the risk of recurrent clots in those with a history of VTE, and reduces healthcare costs. Throughout the guide, the ASH guideline panel used a VTE risk threshold of 2% antepartum and 1% postpartum when deciding whether or not to recommend VTE prophylaxis and specified low molecular weight heparin (LMWH) as the preferred agent for prevention and treatment of pregnancy-associated VTE.

Prophylaxis Dosing

For pregnant women who require prophylaxis, the ASH guideline panel **suggests *against*** intermediate-dose prophylaxis over standard-dose prophylaxis during the antepartum period C. For women who require prophylaxis during the postpartum period, the ASH guideline panel **suggests** either standard- or intermediate-dose LMWH prophylaxis C.

Table 1 – Prophylactic LMWH Dosing

Agent	Standard	Intermediate[1]	Contraindications[2]
Enoxaparin	40 mg/ day	40 mg/ 12hrs or 80 mg once daily	Active major bleeding History of heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies Hypersensitivity to enoxaparin sodium Hypersensitivity to heparin or pork products Hypersensitivity to benzyl alcohol
Dalteparin	5,000 units/day	5,000 units/12hrs or 10,000 units once daily	Active major bleeding History of heparin induced thrombocytopenia (HIT) or HIT with thrombosis Hypersensitivity to dalteparin sodium Hypersensitivity to heparin or pork products Epidural neuraxial anesthesia (see recommendations for management around the time of regional anesthesia)[3]
Tinzaparin	4,500 units/ day or 75 units/ kg once daily for those at extremes of weight	10,000 units once daily	Hypersensitivity to tinzaparin sodium or any of its constituents, including benzyl alcohol (when using multi-dose vials) or sodium metabisulphite[4] History of confirmed or suspected immunologically- mediated heparin-induced thrombocytopenia (HIT) Active major hemorrhage or conditions/ diseases involving an increased risk of hemorrhage Uncontrolled severe hypertension Diabetic or hemorrhagic retinopathy

[1] *Bates SM et al. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis. 2016;41:91-128.*

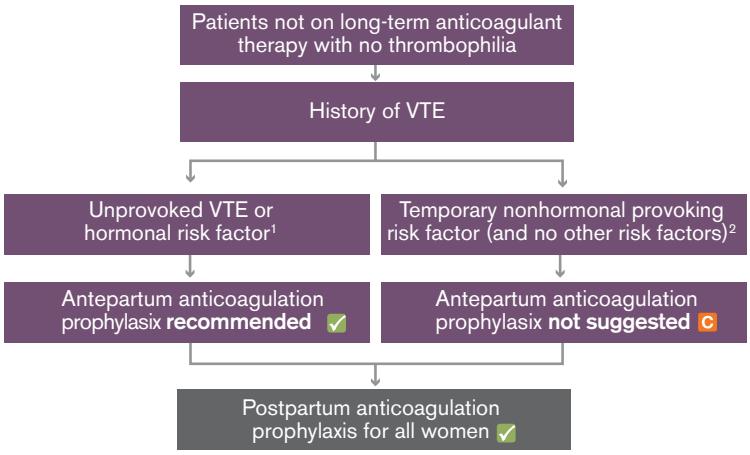
[2] *Selected contraindications per package inserts – see package inserts for full list of contraindications.*

[3] *Horlocker TT, Vandermeuelen E, Kopp SL, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (Fourth Edition). Regional Anesthesia & Pain Medicine. 2018;43:263-309.*

[4] *The 2 mL multi-dose vials of tinzaparin (10,000 anti-Xa IU/mL and 20,000 anti-Xa IU/mL) contain 20 mg of benzyl alcohol as a preservative and must not be given to children <3 years old, premature infants, and neonates, due to risk of gasping syndrome. Benzyl alcohol may cross the placenta, so tinzaparin formulations without benzyl alcohol should be used during pregnancy.*

Prophylaxis for Pregnant Women Not Receiving Long-Term Anticoagulation Therapy

Figure 1



[1] *Hormonal risk factors include pregnancy, postpartum, and hormonal contraception associated with increased VTE risk.*

[2] *Temporary nonhormonal provoking risk factors include surgery, trauma, and prolonged immobilization.*

PROPHYLAXIS IN THE CONTEXT OF INHERITED THROMBOPHILIA

Thrombophilias are laboratory abnormalities associated with an increased risk of VTE. They can be either inherited or acquired and differ in their associated risk of VTE.

Table 2 – When to Offer Prophylaxis in the Context of Thrombophilia

Presentation	Family History of VTE	Antepartum Prophylaxis	Postpartum Prophylaxis
Heterozygous for factor V Leiden mutation	Yes	No ●	No ●
	No	No ●	No ●
Homozygous for factor V Leiden mutation	Yes	Yes ●	Yes ●
	No	Yes ●	Yes ●
Heterozygous for prothrombin mutation	Yes	No ●	No ●
	No	No ●	No ●
Homozygous for prothrombin mutation	Yes	Yes[1] ●	Yes ●
	No	No ●	Yes ●
Protein C deficiency	Yes	No ●	Yes ●
	No	No ●	No ●
Protein S deficiency	Yes	No ●	Yes ●
	No	No ●	No ●
Antithrombin deficiency	Yes	Yes ●	Yes ●
	No	No ●	No ●
Combined thrombophilias	Yes	Yes ●	Yes ●
	No	Yes ●	Yes ●

● = Strong Recommendation ● = Conditional Recommendation

[1] *The ASH guideline panel did not find sufficient evidence to support a formal recommendation or suggestion either for or against antepartum prophylaxis in the context of patients homozygous for prothrombin mutation. The panel consensus was that antepartum prophylaxis is likely appropriate.*

PROPHYLAXIS IN THE CONTEXT OF ASSISTED REPRODUCTIVE THERAPY

Assisted reproduction is associated with an increased risk of VTE. For most women undergoing assisted reproductive therapy, the ASH guideline panel **suggests *against*** anticoagulant prophylaxis to prevent VTE C.

For women undergoing assisted reproductive therapy who develop severe ovarian hyperstimulation syndrome, the ASH guideline panel **suggests** anticoagulant prophylaxis to prevent VTE C.

Diagnosis of VTE in Pregnancy

Pregnant women often have symptoms that are similar to those of DVT and PE. Leg swelling and pain, as well as chest discomfort and shortness of breath, are common during pregnancy and most commonly are not due to VTE. However, physicians must carefully assess women who present with these symptoms and carry out appropriate diagnostic testing if they have clinical concern. There are important implications to missing a diagnosis (risk of fatal PE) or making the wrong diagnosis (unnecessary anticoagulation). Diagnostic tests for PE involve maternal and fetal exposure to radiation. The fetal radiation exposure from diagnostic tests for PE is well below the threshold for harm.

SUSPECTED PULMONARY EMBOLISM

Options available for pulmonary embolism (PE) diagnosis among pregnant women are limited as radiation exposure for the fetus and mother should be limited. ASH guideline panel **suggests** V/Q lung scanning over CT pulmonary angiography (CTPA) C. Evidence is limited for this suggestion, as both options have their own risks and benefits (Table 3).

Table 3 – Comparison of Diagnostic Tools for PE

	V/Q lung scan	CTPA
Pro	Safer for women with respect to breast-absorbed radiation dose and minimizes potential impact on breast cancer risk	Fetal radiation dose lower than with V/Q scanning;[1] CTPA may be indicated in women with abnormal chest radiographs or pre-existing lung disease
Con	May not be as readily available as CTPA in all centers[2]	More radiation exposure to breast compared to V/Q[3]

[1] The difference is dependent on the type of protocol used for both techniques and gestational age with CTPA. Typical fetal radiation doses from V/Q scanning and CTPA are far below the suggested accepted maximal threshold for fetal radiation exposure so there is minimal impact on risk of childhood cancer with either V/Q scan or CTPA.

[2] For centers without access to V/Q lung scanners, CTPA is acceptable.

[3] In this population V/Q and CTPA appear to have equivalent numbers of non-diagnostic scans. Centers should develop pregnancy specific CTPA protocols.

SUSPECTED DEEP VEIN THROMBOSIS (DVT)

For pregnant women with suspected DVT, the ASH guideline panel **suggests** additional investigations, including serial CUS[1] or MRV[2,3], compared to no further investigations after an initial negative ultrasound with imaging of the iliac veins C.

[1] Serial CUS with iliac vein imaging is associated with a low frequency of missed DVT with only 5 of 1000 women (95% CI, 2-25) with negative results expected to present with symptomatic VTE during follow-up.

[2] There is limited evidence suggesting that MRV of the pelvic veins might detect pelvic thrombosis not imaged with Doppler ultrasonography. During first trimester, there does not seem to be an increased harm to the fetus, however the addition of gadolinium at any time during pregnancy may be associated with a small absolute increase in adverse fetal and neonatal outcomes.

[3] In the absence of comparative studies, the panel was not able to recommend one of serial CUS or MRV over the other. Due to the potential association with an increase in the risk of childhood cancer secondary to ionizing radiation combined with the lack of diagnostic utility, venography and CT venography have been superseded by ultrasound scanning and are not usually performed on this patient population.

Treatment of Acute VTE in Pregnancy

Antithrombotic therapy markedly reduces mortality in pregnant and nonpregnant patients with acute VTE. Treatment also reduces the risk of recurrent VTE and post-thrombotic syndrome in those presenting with DVT. In the nonpregnant population, treatment of superficial vein thrombosis reduces the risk of developing DVT or PE; however, similar data are lacking in the pregnant population.

Table 4 – Considerations in Treatment of VTE

Presentation	Options	Action	Comments
Acute VTE	Antithrombotic therapy vs. no therapy	Antithrombotic therapy[1] with LMWH ✅	LMWH has a better safety profile than UFH in this setting. Studies where UFH was used reported more negative outcomes including osteoporotic fracture, risk of spinal fracture, lower bone mineral density measurements 4-7 years after treatment, and HIT. For pregnant women with acute VTE treated with LMWH, the ASH guideline panel **suggests** either once-per-day or twice-per-day dosing regimens.[2,3] C For pregnant women receiving therapeutic LMWH for the treatment of VTE, the ASH guideline panel **suggests *against*** routine monitoring of anti-FXa levels to guide dosing.[4] C
Acute superficial vein thrombosis	Antithrombotic therapy vs. no therapy	Antithrombotic therapy[1] with LMWH C	
Low-risk acute VTE	Initial outpatient therapy vs. hospitalization	Initial outpatient therapy C	This recommendation applies only to low-risk pregnant women with VTE. For those with any high-risk features, the benefit-harm balance would likely favor hospital admission. Vital sign abnormalities, severe pain requiring analgesia, extensive VTE, advanced gestational age, maternal comorbidities that limit tolerance of recurrent VTE or are associated with increased risk of bleeding, contraindications to LMWH, and lack of adequate support at home are all indicators for initial hospitalization.

[1] Data on the use of fondaparinux in pregnancy remain limited, and the use of oral anticoagulants (including vitamin K antagonists and the direct-acting oral anticoagulants) during pregnancy is constrained by concerns about increased risks of pregnancy loss and teratogenicity.

[2] Observational studies in pregnant women showed no clear difference between once-per-day compared to twice-per-day regimens.

[3] Twice daily injections may be considered a burden to some women, but not all. Both options are considered equal and the decision should be made based on patient preference and compliance.

[4] No studies have demonstrated a clear clinical benefit related to dose adjustments and subsequent monitoring. There is a lack of reliability of these tests and there is no validated therapeutic range for LMWH in this population. In the absence of clear benefit with anti-FXa monitoring, there is no need to increase the number of clinic visits for testing. In addition, these tests are resource intensive.

THROMBOLYTIC THERAPY

While standard treatment of VTE involves treatment with anticoagulation, clinicians are often faced with whether or not to escalate to more aggressive therapy for patients that have severe initial clinical manifestations. Thrombolysis involves the use of drugs to dissolve clots immediately. However, the benefits of these drugs must be weighed against the bleeding risks. Thrombolytic drugs can be administered either systemically or locally.

Table 5 – When to Offer Thrombolytic Therapy

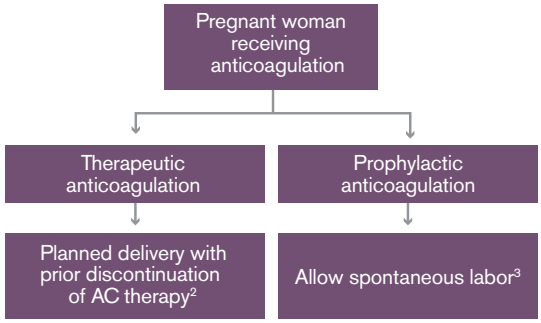
Presentation	Action
Acute PE with hemodynamic instability	For pregnant women with acute PE and life-threatening hemodynamic instability, the ASH guideline panel **suggests** administering systemic thrombolytic therapy in addition to anticoagulant therapy C
Acute PE without hemodynamic instability	For pregnant women with acute PE and right ventricular dysfunction without hemodynamic instability, the ASH guideline panel **suggests *against*** the addition of systemic thrombolytic therapy to anticoagulation compared with anticoagulation alone C
Acute lower-limb DVT	For pregnant women with acute lower extremity DVT, the ASH guideline panel **suggests *against*** the addition of catheter-directed thrombolysis to anticoagulation C

Delivery and Breastfeeding

ANTICOAGULATION AND DELIVERY

A multidisciplinary, individualized approach should be used when decisions are made about delivery plans and anesthetic options for women receiving anticoagulants. Shared decision making is required when peridelivery management in women receiving anticoagulation and its potential impact on access to neuraxial anesthesia is being considered.[1]

Figure 2



[1] Current North American and European anesthetic guidelines call for at least a 12-hour interval between the last dose of prophylactic LMWH and placement of an epidural catheter. For patients receiving intermediate-dose prophylaxis, that interval is increased to 24 hours.

[2] Conditional recommendation C. Planned delivery is defined as either induction of labor or elective cesarean section as per obstetric indications. Induction of labor does not appear to increase the risk of neonatal or maternal complications.

[3] Conditional recommendation C. Allowing spontaneous onset labor may minimize the need for medical intervention in labor. The panel considered that the 12-hour recommended interval between the last dose of standard prophylactic-dose LMWH and placement of an epidural catheter would allow most women receiving standard prophylactic-dose LMWH the option of neuraxial anesthesia, regardless of whether delivery was scheduled or spontaneous. Patients and their caregivers who place a very high priority on access to an epidural may prefer planned delivery. Allowing spontaneous onset of labor may have an impact on access to neuraxial analgesia (epidural analgesia or spinal anesthesia).

ANTICOAGULATION AND BREASTFEEDING

When considering safe use of anticoagulants while breastfeeding, the general principle is that one would like to avoid those drugs that are both excreted into the breast milk and have the potential for oral absorption by the infant. Women who are breastfeeding and have an indication for anticoagulation should not use direct-acting oral anticoagulants (DOACs). Instead, they should use UFH, LMWH, warfarin, acenocoumarol, fondaparinux, or danaparoid ✅.

Table 6 – Anticoagulants Considered Safe in the Context of Breastfeeding

Drugs to use	Drug Levels in Breast Milk
UFH[1]	Undetectable
LMWH[1]	Detectable (low) but not orally absorbed
Warfarin[1]	Undetectable
Acenocoumarol[1]	Undetectable
Danaparoid	Undetectable
Fondaparinux	Data Unavailable; unlikely to be orally absorbed

[1] The agents with greatest experience in this patient population and the best evidence for safety were warfarin, acenocoumarol, LMWH, and UFH.

Table 7 – Anticoagulants Considered Unsafe in the Context of Breastfeeding

Drugs not to use	Drug Levels in Breast Milk
Rivaroxaban	Detectable (low)
Other DOACs[2]	Data Unavailable

[2] It is possible that DOACs are safe, but until further evidence and experience are available, clinicians should avoid prescribing these agents to women who are breastfeeding.

Strength of Recommendations and Quality of Evidence

The methodology for determining the strength of each recommendation and the quality of the evidence supporting the recommendations was adapted from GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Guyatt GH, et al; GRADE Working Group. 2008;336(7650):924–926. More details on this specific adaptation of the GRADE process can be found in American Society of Hematology 2018 Guidelines for Management of Venous Thromboembolism: Venous Thromboembolism in the Context of Pregnancy.[1]

Strength of Recommendation	
✓	**Strong recommendations** - Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
C	**Conditional recommendations** - Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.

How to Use This Pocket Guide

ASH pocket guides are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. The information included in this guide is not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the unique clinical presentation of an individual patient, ideally though a shared process that considers the patient's values and preferences with respect to all options and their possible outcomes. Decisions may be constrained by realities of a specific clinical setting, including but not limited to institutional policies, time limitations, or unavailability of treatments. ASH pocket guides may not include all appropriate methods of care for the clinical scenarios de-scribed. As science advances and new evidence becomes available, these pocket guides may become obsolete. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

The complete American Society of Hematology 2018 Guidelines for Management of Venous Thromboembolism: Venous Thromboembolism in the Context of Pregnancy[1] include additional remarks and contextual information that may affect clinical decisionmaking.
To learn more about these guidelines, visit ***hematology.org/VTEguidelines***.

Conflict of interest information for Drs. Bates, Rajasekhar, and McLintock may be found at ***hematology.org/pocketguidesCOI***.

[1] *Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism:*

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For expert consultation on VTE in the context of pregnancy and other hematologic questions, submit a request to the ASH Consult a Colleague program at ***www.hematology.org/consult*** (ASH members only).