Thrombophilia Screening, Diagnosis and Anticoagulation:
Antepartum and Postpartum Management

February 2024

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Screening and Management Recommendations

Introduction

- Venous Thromboembolic Events (VTE)- includes deep vein thrombosis (DVT) and pulmonary embolism (PE)
- Incidence of VTE: 0.5-2.0 per 1000 pregnancies
- 75-80% are DVT and 20-25% are PE
- Highest risk time is postpartum

Two types of Thrombophilias:

1. Inherited
   - Factor V Leiden mutation
   - Prothrombin Gene mutation
   - Antithrombin deficiency
   - Protein C deficiency
   - Protein S deficiency
2. Acquired
   - Lupus anticoagulant
   - Beta 2 glycoprotein antibody
   - Anticardiolipin antibody

Inherited Thrombophilias: Who should be screened?

- Personal history of VTE
- First degree relative (parent or sibling) with a history of an inherited high-risk thrombophilia or VTE before age 50 in absence of other risk factors.
- Screening for inherited thrombophilias is otherwise not recommended for recurrent fetal loss, placenta abruption, FGR, or pre-eclampsia. Treatment prevents thromboembolism but has NOT been shown to prevent or improve other adverse pregnancy outcomes.

Table 1. Risk of Venous Thromboembolism with Different Inherited Thrombophilias

	Prevalence in General Population (%)	VTE Risk Per Pregnancy (No History) (%)	VTE Risk Per Pregnancy (Previous VTE) (%)	Percentage of All VTE
Factor V Leiden heterozygote	1-15	0.5-3.1	10	40
Factor V Leiden homozygote	<1	2.2-14.0	17	2
Prothrombin gene heterozygote	2-5	0.4-2.6	>10	17
Prothrombin gene homozygote	<1	2-4	>17	0.5
Factor V Leiden/prothrombin double heterozygote	0.01	4-8.2	>20	1-3
Antithrombin deficiency	0.02	0.2-11.6	40	1
Protein C deficiency	0.2-0.4	0.1-1.7	4-17	14
Protein S deficiency	0.03-0.13	0.3-6.6	0-22	3

(ACOG, 2018)

Inherited Thrombophilias: Diagnostic Testing

Ideally should be done ≥ 6 weeks from thrombosis, while not pregnant, and while not taking anticoagulation.

Screening should be limited to the above thrombophilias. Screening for MTHFR mutation and homocysteine levels is NOT recommended. MTHFR mutation does not appear to convey increased risk for VTE in either pregnant or non-pregnant women. Other thrombophilias have been described, including alternative factor V variations, mutations of PAI-1 genes, and protein Z deficiency among others. There is insufficient evidence to recommend testing for these alternative thrombophilias and screening is NOT recommended. If such testing has been obtained, no modification of clinical care is recommended based on these results.

Table 2. How to Test for Inherited Thrombophilias

Thrombophilia	Testing Method	Is Testing Reliable During Pregnancy?	Is Testing Reliable During Acute Thrombosis?	Is Testing Reliable with Anticoagulation?
Factor V Leiden mutation	Activated protein C resistance assay (second generation) If abnormal: DNA analysis	Yes Yes	Yes Yes	No Yes
Prothrombin G20210A mutation	DNA analysis	Yes	Yes	Yes
Protein C deficiency	Protein C activity (<65 %)	Yes	No	No
Protein S deficiency	Functional assay (<55%)	No*	No	No
Antithrombin deficiency	Antithrombin activity (<60%)	Yes	No	No

*If screening in pregnancy is necessary, cutoff values for free protein S antigen levels in the second and third trimesters have been identified at less than 30% and less than 24%, respectively.
(ACOG, 2018)

Acquired Thrombophilias: Who should be screened?

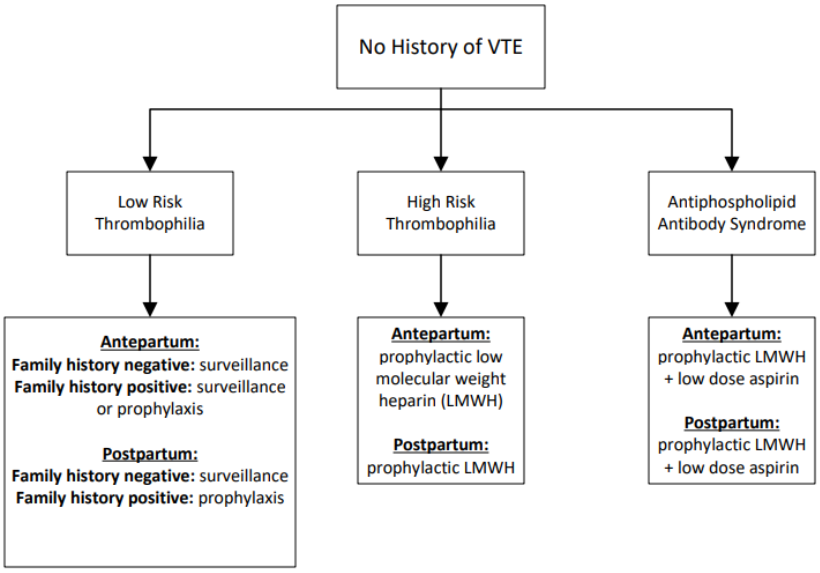
- ≥ 3 unexplained consecutive spontaneous abortions less than 10 weeks gestation (aneuploidy causes excluded)
- ≥ 1 fetal death at or beyond 10 weeks gestation (morphologically normal fetus)
- ≥ 1 severe preeclampsia, eclampsia, or placental insufficiency requiring delivery at < 34 weeks gestation
- Unexplained venous or arterial thrombosis in any tissue/organ
- Small vessel thrombosis in any location without evidence of vessel wall inflammation

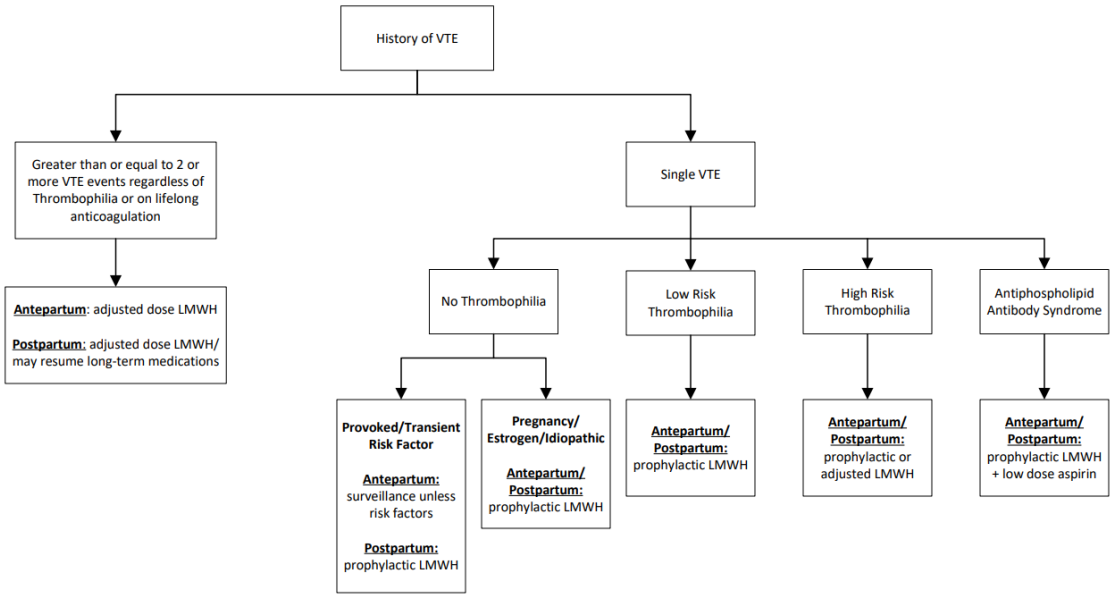
Acquired Thrombophilias: Diagnostic Laboratory Testing Criteria

- Lupus Anticoagulant on 2 or more occasions at least 12 weeks apart
  - Either present or absent
- Anticardiolipin Antibody of IgG or IgM present in titer of > 40 gpl or mpl, or > 99%ile on 2 or more occasions at least 12 weeks apart
- Beta2 glycoprotein Antibody of IgG or IgM present on 2 or more occasions at least 12 weeks apart
- Antiphospholipid Antibody Syndrome requires at least 1 clinical criterion (See "who should be screened") and 1 laboratory criteria for diagnosis

Risk Assessment and Management Guidelines: Antepartum (AP) and 6 weeks Postpartum (PP)

- PP anticoagulation should always be equal or greater than AP anticoagulation
- Low dose aspirin is not indicated unless specifically stated
- **Low risk Thrombophilias**: Factor V Leiden heterozygous, Prothrombin heterozygous, Protein C Deficiency, Protein S deficiency
- **High risk Thrombophilias:** Factor V Leiden or Prothrombin homozygous, Compound Heterozygote for Prothrombin and Factor V Leiden, Antithrombin Deficiency
- Family History refers to 1st degree relative with VTE
- Other risk factors: obesity, prolonged immobilization, or cesarean delivery





*Intermediate dosing of anticoagulation is not typically used but can be considered in appropriate patients per physician judgement and patient counseling.

Anticoagulation: Dosing and Monitoring

General Principles

- Low molecular weight heparin (LMWH) is the preferred choice for prevention and treatment of VTE secondary to ease of administration, predictable dose-response, and better safety profile
    - Patients may remain on LMWH if delivery is predictable
    - If delivery is threatened or unpredictable in a patient on therapeutic dosing and patient is hospitalized, therapeutic subcutaneous LMWH should be discontinued in favor of intravenous unfractionated heparin (UFH)
- Increase in VTE risk occurs as early as first trimester; initiation of anticoagulation should occur upon confirmation of a viable pregnancy
- Maternal actual weight is used in adjusted (therapeutic) dosing regimens
- Dosage influenced by severity of thrombophilia and other risk factors
- LMWH is not recommended in patients with renal failure (creatinine > 1.5) or with active hemorrhage, or in patients likely to require thrombolytic therapy or emergency surgery

- Oral anti-Xa medications and Vitamin K antagonists (Warfarin) are not recommended for use in pregnancy
    - Exception is prevention of thromboembolism in patients with mechanical heart valves: may benefit from warfarin after risk/benefit discussion with MFM/Cardiology.
- Unfractionated Heparin, low molecular weight heparin, and warfarin are acceptable during breastfeeding

Table 4. Anticoagulation Regimen Definitions

Anticoagulation Regimen	**Anticoagulation Dosage**
Prophylactic LMWH*	Enoxaparin, 40 mg SC once daily Dalteparin, 5,000 units SC once daily Tinzaparin, 4,500 units SC once daily Nadroparin, 2,850 units SC once daily
Intermediate-dose LMWH	Enoxaparin 40 mg SC every 12 hours Dalteparin 5,000 units SC every 12 hours
Adjusted dose (therapeutic) LMWH±	Enoxaparin, 1 mg/kg every 12 hours Dalteparin, 200 units/kg once daily Tinzaparin, 175 units/kg once daily Dalteparin, 100 units/kg every 12 hours Target an anti-Xa level in the therapeutic range of 0.6-10 units/mL 4 hours after last injection for twice-daily regimen; slightly higher doses may be needed for a once-daily regimen
Prophylactic UFH	UFH, 5,000-7,500 units SC every 12 hours in first trimester UFH, 7,500-10,000 units SC every 12 hours in the second trimester UFH, 10,000 units SC every 12 hours in the third trimester, unless the aPTT is elevated
Adjusted dose (therapeutic) UFH±	UFH, 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5-2.5 x control) 6 hours after injection
Postpartum anticoagulation	Prophylactic, intermediate, or adjusted dose LMWH for 6-8 weeks as indicated. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.
Surveillance	Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep vein thrombosis or pulmonary embolism. VTE risk assessment should be performed prepregnancy or early in pregnancy and repeated if complications develop, particularly those necessitating hospitalization/prolonged immobility.

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SC, subcutaneously; UFH, unfractionated heparin; VTE, venous thromboembolism.
*Although at extremes of body weight, modification of dose may be required.
±Also referred to as weight-adjusted, full treatment dose.
(ACOG, 2018)

Monitoring Levels

- If on prophylactic anticoagulation, monitoring of therapeutic levels is not indicated.
- Monitoring therapeutic levels is generally not recommended if actual weight-based dosing is used.
- In particularly high-risk patients, those suspected of non-compliance, or those at extremes of weight, obtaining an Anti Xa level may be considered.
  - LMWH: Check Anti-Xa 4-6 hours after 3rd dose; therapeutic levels 0.6-1.1 U/mL
  - UFH: Check Anti-Xa 4-6 hours after 3rd dose; therapeutic level 0.35-0.7 U/mL
- Complications with Heparin Use: (All complications less frequent with LMWH vs UFH)
- Bleeding, Skin necrosis, Osteoporosis
- Heparin Induced Thrombocytopenia (HIT)
  - Very rare in pregnancy but potentially life/limb threatening.
  - Stop treatment if platelets less than 100,000 and consult hematology for possible alternative therapy.

Intrapartum and Postpartum Management

- **Induction of Labor**
  Patients on Anticoagulation outpatient should be instructed to discontinue as follows in preparation for delivery based on Society for Obstetric Anesthesia and Perinatology Consensus Statement on Anesthetic Management of Pregnant and Postpartum Women receiving anticoagulation:
  - **UFH:**
    - On doses 5000u BID: discontinue 4-6hrs prior to regional anesthesia and obtain aPTT
    - On doses 7500u BID: discontinue ≥ 12 hours prior to regional anesthesia and obtain aPTT
    - On doses 10000u BID: discontinue ≥ 12-24 hours prior to regional anesthesia and obtain aPTT
  - **LMWH:**
    - Adjusted/Therapeutic Dose: Discontinue 24 hours prior to regional anesthesia (on day prior, take am dose but hold evening dose)
    - Prophylactic dose: Discontinue 12 hours prior to regional anesthesia.

- **Spontaneous Labor**
  If necessary, in select cases reversal of therapeutic heparin anticoagulation may be accomplished with protamine sulfate. UFH is fully reversible and LMWH is 60-80% reversible.
    - Protamine sulfate use is contraindicated in patients who have shown previous intolerance to the drug or with salmon sperm allergy.
    - If labor begins unexpectedly in a fully anticoagulated patient, most patients will not have excessive intrapartum bleeding. Reversal of heparin is rarely required and is not indicated for prophylactic doses.
- **Post-partum management**
    - Postpartum anticoagulation should always be equal to or greater than antepartum anticoagulation.
    - Do not initiate anticoagulation sooner than 4-6 hours after vaginal delivery and 6-12 hours after cesarean delivery.
    - If patients require heparin drip postoperatively, timing should be individualized in conjunction with hematology recommendations.
    - UFH
        - Catheter removal can occur ≥ 4-6 hours after a dose of UFH and subsequent UFH dosing should occur ≥ 1 hour after catheter removal.
        - For IV UFH, wait ≥ 1hr after neuraxial block (if no signs of postpartum hemorrhage) before initiating or restarting anticoagulation.
    - LMWH
        - Catheter removal can occur ≥ 12 hours after a dose of LMWH and subsequent LMWH dosing should occur ≥ 4 hours after catheter removal.
        - For higher therapeutic dose LMWH, consider waiting ≥ 24hrs after the neuraxial procedure and ≥ 4 hours after epidural catheter removal before initiating or restarting LMWH.
    - Warfarin therapy should be stopped 5 days before surgery and restarted 12-24 hours postoperatively.

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SmartSet Committee: January 2026