November 2021

Venous Thromboembolism, Thrombophilia Screening, and Anticoagulation: Antepartum and Postpartum Management

I: Screening and Management Recommendations

Introduction:

1. Venous Thromboembolic Events (VTE)-includes DVT and PE
2. Incidence of VTE: 0.6-2.0 per 1000 pregnancies
3. DVT 3 times more likely than PE
4. Occurs equally among trimesters; 5 times more likely postpartum
5. Deaths usually occur postpartum, within 30 minutes from the event.

Inherited Thrombophilias: Who Should Be Screened

1. Personal history of VTE
2. First degree relative (parent or sibling) with history of an inherited high-risk thrombophilia (Antithrombin deficiency, Factor V Leiden Homozygous, Prothrombin Homozygous, or Compound Heterozygous for FVL and Prothrombin), or VTE before age 50 in absence of other risk factors.
3. Screening for inherited thrombophilias is otherwise not recommended for recurrent fetal loss, placental abruption, FGR, or pre-eclampsia.
    a. Treatment prevents thromboembolism but has NOT been shown to prevent or improve other adverse pregnancy outcomes
4. Highest risk with Antithrombin deficiency, followed by Factor V Leiden/ prothrombin double heterozygote (see table 1 from ACOG PB #197)

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	References
Factor V Leiden heterozygote	1–15	0.5–3.1	10	40	1–4, 11, 12
Factor V Leiden homozygote	<1	2.2–14.0	17	2	1–4, 11, 12
Prothrombin gene heterozygote	2–5	0.4–2.6	>10	17	1–4, 11, 12
Prothrombin gene homozygote	<1	2–4	>17	0.5	1–4, 11, 12
Factor V Leiden/ prothrombin double heterozygote	0.01	4–8.2	>20	1–3	1–4, 12
Antithrombin deficiency	0.02	0.2–11.6	40	1	1, 5, 6, 11, 12
Protein C deficiency	0.2–0.4	0.1–1.7	4–17	14	1, 5, 7, 11, 12
Protein S deficiency	0.03–0.13	0.3–6.6	0–22	3	1, 8–12

Acquired Thrombophilias: Who Should Be Screened

Screen for Lupus Anticoagulant and Anticardiolipin Antibodies in patients with:

1. ≥3 unexplained consecutive spontaneous abortions <10 wks gestation (hormonal, aneuploidy causes excluded)
2. ≥1 fetal deaths at or beyond 10 wks gestation (morphologically normal fetus)
3. ≥1 Severe preeclampsia, eclampsia or placental insufficiency requiring delivery <34 wks gestation

4. Unexplained venous or arterial thrombosis in any tissue/organ
5. Small vessel thrombosis in any location without evidence of vessel wall inflammation.

Inherited Thrombophilia Work-up: Should be done ≥6 weeks from thrombotic event, while patient is not pregnant, and while not taking anticoagulation. (see table 2 from ACOG PB #197)

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 Anti-coagulation?
Factor V Leiden mutation	Activated protein C resistance assay (second generation)	Yes	Yes	No
	If abnormal: DNA analysis	Yes	Yes	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.

Acquired Thrombophilias Work-up: Antiphospholipid antibody syndrome

Criteria for diagnosis: must have at least 1 laboratory and 1 clinical criteria (see "Acquired Thrombophilias: Who should be Screened"

Laboratory criteria:

1. Lupus anticoagulant on 2 or more occasions at least 12 weeks apart
    - Either present or absent
2. Anticardiolipin antibody of IgG or IgM present in titer >40 gpl or mpl or greater than 99%ile on 2 or more occasions at least 12 weeks apart
3. Anti-B2 glycoprotein I of IgG or IgM >99%ile as defined by laboratory, present on 2 or more occasions at least 12 weeks apart

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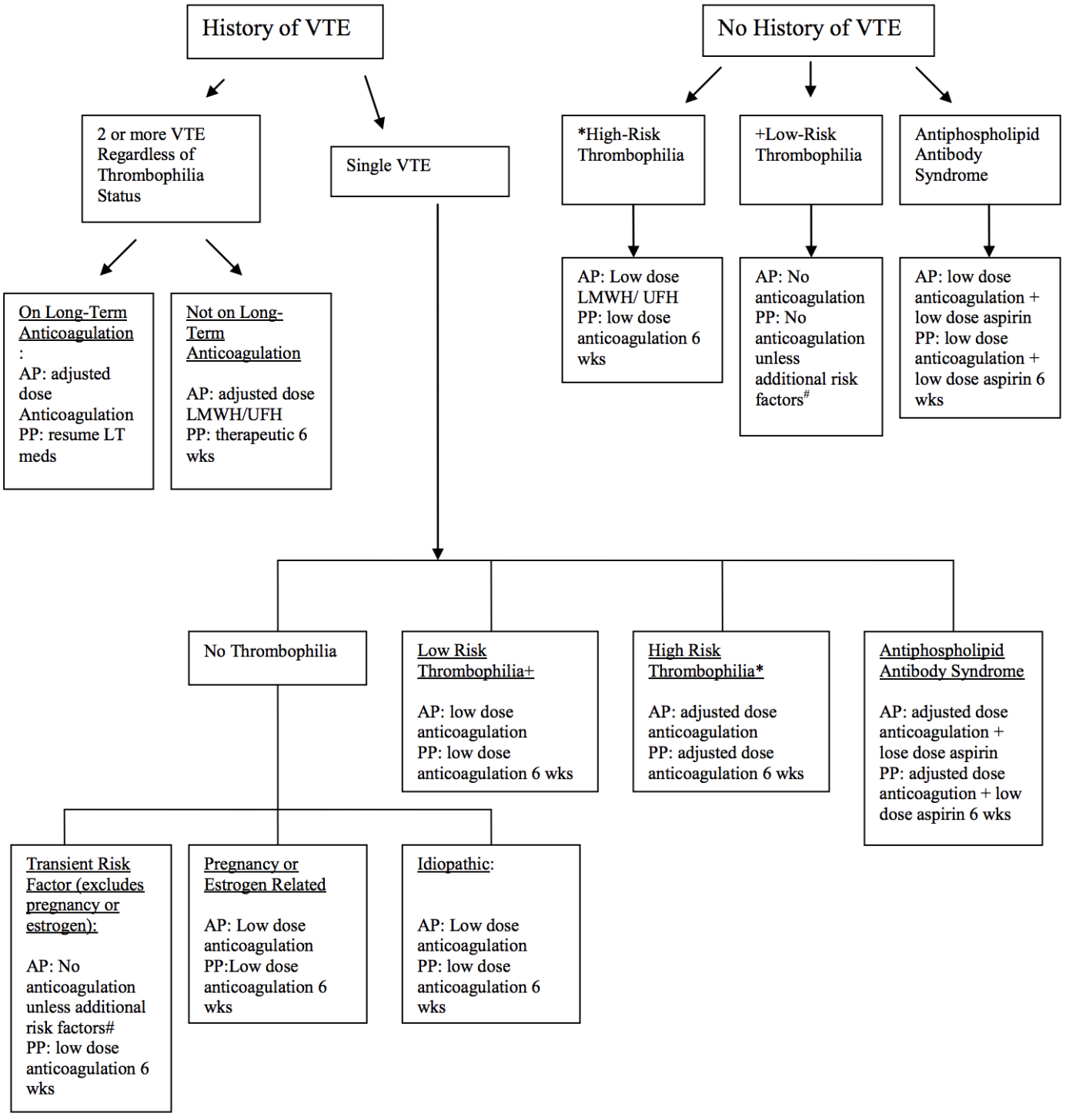
Risk Assessment and Management Guidelines: Antepartum (AP) and 6 weeks Postpartum (PP)

-PP anticoagulation should always be equal to or greater than AP anticoagulation
-Low-dose aspirin is not indicated unless specifically stated



*High Risk Thrombophilia: Antithrombin deficiency, Factor V Leiden Homozygous, Prothrombin Homozygous, Compound heterozygous for FVL/Prothrombin
+Low Risk Thrombophilia: Factor V Leiden Heterozygous, Prothrombin Heterozygous, Protein C or S deficiency
#Risk Factors: First degree relative with VTE <50 years of age, obesity, cesarean, prolonged immobility

*High Risk Thrombophilia: Antithrombin deficiency, Factor V Leiden Homozygous, Prothrombin Homozygous, Compound heterozygous for FVL/Prothrombin
+Low Risk Thrombophilia: Factor V Leiden Heterozygous, Prothrombin Heterozygous, Protein C or S deficiency
#Risk Factors: First degree relative with VTE <50 years of age, obesity, cesarean, prolonged immobility

Other Considerations for Antepartum Management in Antiphospholipid Antibody (APLA) Syndrome

1. Patients with APLA Syndrome receive ultrasound q4 weeks after 20 wks to assess fetal growth, and fetal testing starting at 32 weeks unless clinically indicated sooner
2. Patients with a low risk thrombophilia and family (but no personal) history of VTE, should receive postpartum low dose anticoagulation but no anticoagulation antepartum

II. Anticoagulation: Dosing and Monitoring

General Principles:

1. 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.
2. Initiation of anticoagulation should occur upon pregnancy confirmation
3. Maternal weight used in adjusted (therapeutic) dosing regimens
4. Dosage influenced by severity of thrombophilia and other risk factors (obesity, cesarean delivery, family history, history of VTE)
5. 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.
6. If delivery is threatened or unpredictable and patient is hospitalized, therapeutic SC anticoagulation is discontinued and IV UFH is instituted.
7. **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**
8. **Unfractionated heparin, low molecular weight heparin, and warfarin are acceptable during breastfeeding**

Medication Dosing

Anticoagulant	**Dosing**	**Notes**
Lovenox (LMWH)	**Prophylactic**: 40 mg SQ daily **Intermediate:** 40 mg SQ BID **Adjusted/Therapeutic**: 1 mg/kg q 12 hours	May need to be adjusted at extremes of body weight
Unfractionated heparin	**Prophylactic** • **1st trimester:** 5,000-7,500u SQ BID • **2nd trimester:** 7,500-10,000u SQ BID • **3rd trimester:** 10,000u SQ BID **Adjusted/Therapeutic:** 10,000 SQ or more adjusted to target aPTT 1.2-1.5 x control 6 hours after injection	

Coumadin	**Starting:** 5 mg daily x 2 days • Adjust dose by 2.5-5 mg daily to achieve INR of 2-3 for 2 days • Continue adjusted dose LMWH/UFH for at least 5 days until INR is therapeutic. • Check INR/CBC weekly • **Refer to hematology for follow up**	Postpartum only unless mechanical valve

Monitoring Levels

If on prophylactic anticoagulation, monitoring of levels is not indicated

Recommend following anti-Xa levels for adjusted dosing regimens at least every trimester

1. LMWH: Check anti-Xa 4-6 hours after 3rd dose; therapeutic level 0.6-1.0 U/mL; increase/decrease dose 10-25% as needed to achieve level; once therapeutic recheck monthly
2. UFH: Check anti-Xa 4-6 hours after 3rd dose; therapeutic level 0.35-0.7 U/mL; increase/decrease dose 10-25% as needed to achieve level
3. Weekly assessment of platelet count first 3 weeks after initiating heparin
4. In the morbid obese, consider changing sites if difficulty achieving level.

Complications with Heparin Use:

Bleeding, Skin necrosis, Osteoporosis

Heparin Induced Thrombocytopenia (HIT)

- Very rare in pregnancy but potentially life and limb threatening
- Stop Treatment if platelets <100,000 and consult Hematologist for alternative therapy

III. Intrapartum and Postpartum Management

1. Induction of Labor

Patients on Anticoagulation outpatient should be instructed to discontinue as follows:

A. UFH

1. ***Adjusted/Therapeutic dose***: Discontinue 12 hours prior to induction of labor (i.e. on day prior may take am dose but not pm dose)
2. ***Low/Prophylactic dose:*** May continue until presents for induction. (i.e. may take both doses on day prior)

B. LMWH

1. ***Adjusted/Therapeutic dose***: Discontinue 24 hours prior to delivery (i.e. on day prior do not take evening dose or am dose the morning of induction, surgery)
2. ***Low/Prophylactic dose:*** Discontinue 12 hours prior to delivery (i.e. on day prior, may take am dose but hold evening dose)

2. Spontaneous Labor -If necessary, reversal of **therapeutic** heparin anticoagulation may be accomplished with protamine sulfate. Only minimally effective in LMWH.

A. Protamine sulfate use is contraindicated in patients who have shown previous intolerance to the drug or with salmon sperm allergy.

B. If labor begins unexpectedly in a fully anticoagulated pregnancy, most patients will not have excessive intrapartum bleeding. Reversal of heparin is rarely required, and is not indicated for prophylactic doses.
   a. Low dose anticoagulation reversal not indicated

3. Admission for C-section

A. The American Society of Regional Anesthesia and Pain Medicine recommends that spinal/epidural anesthesia should not be given until 12 hours after administration of a prophylactic dose of LMWH, 24 hours after the last therapeutic LMWH dose, and 12 hours after the last therapeutic subcutaneous unfractionated heparin dose (if patient on UFH and aPTT normal, regional anesthesia acceptable).

B. Society for Obstetric Anesthesia and Perinatology Consensus Statement on Anesthetic Management of Pregnant and Postpartum Women Receiving Anticoagulation (2017):

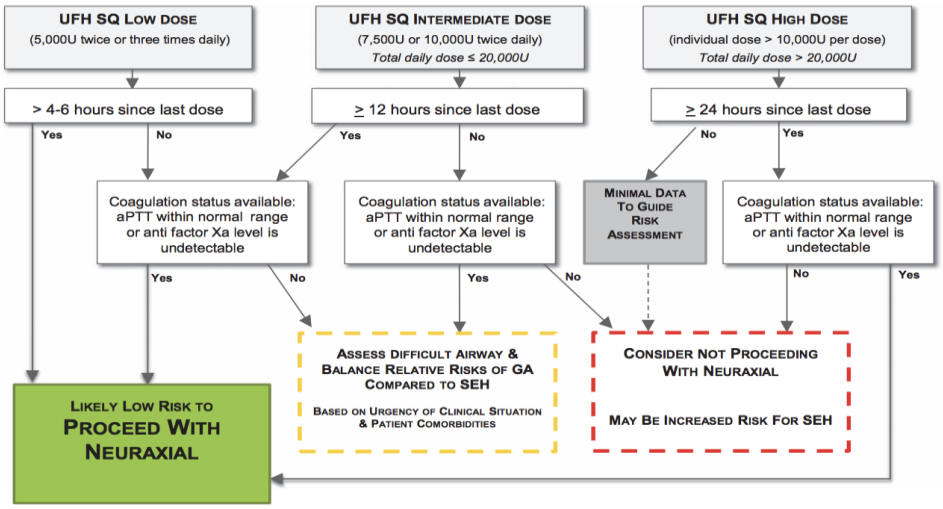


Figure 3. Decision aid for urgent or emergent neuraxial procedures in the obstetric patient receiving UFH. *Assume normal renal function, body weight > 40 kg, and no other contraindications to neuraxial anesthesia. aPTT indicates activated partial thromboplastin time; GA, general anesthesia; SEH, spinal epidural hematoma; SQ, subcutaneous; UFH, unfractionated heparin. Note: This SOAP consensus statement is not intended to set out a legal standard of care and does not replace medical care or the judgment of the responsible medical professional considering all the circumstances presented by an individual patient.

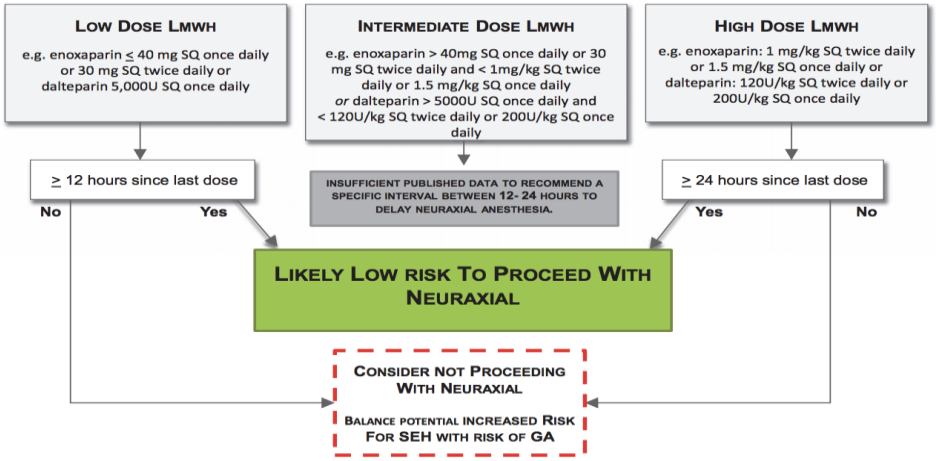


Figure 4. Decision aid for urgent or emergent neuraxial procedures in the obstetric patient receiving LMWH. *Assume normal renal function, body weight >40 kg, and no other contraindications to neuraxial anesthesia. GA indicates general anesthesia; LMWH, low molecular weight heparin; SEH, spinal epidural hematoma; SQ, subcutaneous. Note: This SOAP consensus statement is not intended to set out a legal standard of care and does not replace medical care or the judgment of the responsible medical professional considering all the circumstances presented by an individual patient.

4. Post Partum Management

A. Post Partum anticoagulation should always be equal to or greater than antepartum anticoagulation.
B. Do not initiate anticoagulation sooner than 4-6 hours after vaginal delivery and 6-12 hours after cesarean section

C. **Restarting heparin drip post operatively should be individualized in conjunction with hematology recommendations**
D. UFH
    a. Catheter removal can occur ≥4–6 hours after a dose of UFH and subsequent UFH dosing should occur ≥1 hour after catheter removal
    b. For IV UFH, wait ≥1 hour after neuraxial block (if no signs of postpartum hemorrhage) before initiating or restarting anticoagulation
E. LMWH
    a. Catheter removal can occur ≥12 hours after a LMWH dose and subsequent LMWH dosing should occur ≥4 hours after catheter removal
    b. For higher dose LMWH (eg, enoxaparin 1 mg/kg SQ twice daily or 1.5 mg/kg SQ once daily; dalteparin 120 U/kg SQ twice daily or 200 U/kg SQ once daily), consider waiting ≥24 hours after the neuraxial procedure and ≥4 hours after epidural catheter removal before initiating or restarting LMWH therapy
F. Warfarin therapy should be stopped five days before surgery and restarted 12 to 24 hours postoperatively.

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