Physiologic and anatomic changes in pregnancy result in an acquired thrombophilic state that increases the risk of venous thromboembolism (VTE) to five times that of a non-pregnant woman. Pregnancy related changes include hypercoagulability, increased venous stasis, decreased venous flow, compression of the pelvic veins and inferior vena cava by the enlarged uterus, and decreased mobility. VTE complicates 1 in 1400 pregnancies and accounts for 11% of maternal deaths in the United States, most of which occur in the postpartum period. (Lockwood & Werner, 2010) Even though there is an increased risk of VTE in women during pregnancy and the postpartum period, prophylactic anticoagulation for all pregnant women as a routine is not recommended. (ACOG, 2011 reaffirmed 2014)

A personal history of thrombosis is the most important individual risk factor for VTE increasing a woman's risk for recurrent VTE three to fourfold. 15-25% of all cases of VTE in pregnancy are recurrent events. (ACOG, 2011 reaffirmed 2014) Another important risk factor for VTE in pregnancy is the presence of an inherited or acquired thrombophilia. Other factors putting a pregnant woman at risk include obesity, hemoglobinopathies, hypertension, smoking, and operative delivery.

The most common site for a deep vein thrombosis (DVT) in pregnancy is the left lower extremity. The two most common signs (80% of cases) of a DVT include pain and swelling of an extremity. (ACOG, 2011 reaffirmed 2014) A difference in calf circumference of 2 cm or more is suggestive of a DVT. Compression ultrasound of the proximal veins (femoral and popliteal) is the recommended diagnostic test. Routine surveillance is reasonable with a negative test result, however, if an iliac vein thrombosis is suspected, further imaging should be considered.

Signs and symptoms suggestive of pulmonary embolism (PE) include shortness of breath, chest pain, tachypnea, and decreased oxygen saturation. Diagnosis of a PE can be made through computed tomographic (CT) angiography which is associated with relatively low radiation level exposure to the fetus. While ventilation perfusions scans were once the diagnostic test of choice for diagnosis of pulmonary embolism, CT angiography has largely supplanted this technology because of the better sensitivity and specificity of CT.

Acquired Thrombophilias

Antiphospholipid syndrome (APS) is an acquired thromboplic condition in which an individual makes antibodies against phospholipids which results in VTE. Up to 20% of individuals with VTE are found to have acquired thrombophilias. Acquired thrombophilias are associated with fetal loss, abruption, severe pre-eclampsia, and IUGR.

Diagnosis of APS requires fulfillment of BOTH clinical AND laboratory criteria. Clinical criteria for diagnosis of APS requires a history of at least one of the following:(ACOG, 2012 reaffirmed 2015; Lockwood & Werner, 2010)

- Thrombosis in any tissue or organ except superficial venous thrombosis.
- At least one fetal death at or beyond the 10th week of gestation.
- At least one preterm birth at or before 34 weeks of gestation due to pre-eclampsia or placental insufficiency.*
- At least 3 consecutive spontaneous abortions before the 10th week of gestation.

*Although preterm severe preeclampsia and early onset of placental insufficiency are part of the clinical criteria for the diagnosis of APS, insufficient evidence exists to support that screening and treatment of women with these conditions improves subsequent pregnancy outcomes. (ACOG, 2012 reaffirmed 2015)

Laboratory tests for APS diagnosis include:

- Lupus anticoagulant activity detected.
- Anticardiolipin antibodies (IgG and IgM at moderate or high positive titers).
- Anti-β2-glycoprotein I antibodies (IgG and IgM at high positive titer).
- Positive results for any of the above tests should be repeated after 12 weeks or more to confirm persistence.

The significance of other APS antibodies or isotypes (antiphosphatidylserine, IgA, etc) are unknown and should not be routinely ordered as part of workup for APS.

Patients who meet laboratory and clinical criteria should be diagnosed with APS and educated on signs and symptoms of VTE. Given the increased risk of adverse pregnancy outcomes, treatment is recommended and depends upon the patient's personal history. See table 1: "Indications and Duration of Outpatient Anticoagulation Use in Pregnancy".

Pregnancy monitoring for Patients with APS

- Targeted/comprehensive ultrasound is NOT needed in the absence of other risk factors.
- Monitor fetal growth q 4-6 weeks with ultrasound beginning at 24 weeks; if IUGR is suspected, more frequent ultrasound measurements with Doppler assessment of the umbilical artery is indicated. Maternal Fetal Medicine consultation should be sought to assist in the assessment and to determine optimal timing of delivery.
- Assessment for signs and symptoms of pre-eclampsia. Patients with risk factors for pre-eclampsia, in addition to APS, should have office visits every 2-3 weeks beginning at 24 weeks.
- There is insufficient evidence to recommend routine antenatal testing in the absence of complications, other co-morbidities, or history of adverse pregnancy outcomes.

Peripartum Management for Patients with APS

Uncomplicated pregnancies with a diagnosis of APS should be delivered at 39 weeks. Pregnancies complicated by IUGR, pre-eclampsia or any maternal co-morbidities should be delivered earlier based on clinical indications. In order to facilitate the availability of regional anesthesia, patients on thromboprophylaxis (PPx) with Low Molecular Weight Heparin (LMWH) should be transitioned to Unfractionated Heparin (UFH) 7500-10,000 units SQ BID at 36 weeks since regional anesthesia is contraindicated within 18-24 hrs of LMWH.

Postpartum Management for Patients with APS

Following delivery, there remains a risk of VTE for patients with APS and therefore thromboprophylaxis with heparin should be continued although aspirin therapy may be discontinued.

- Anticoagulation should not be initiated within 4 hours of epidural removal to reduce the risk of an epidural hematoma.
- Vaginal delivery: restart UFH or LMWH at least 6 hrs after delivery.
- Cesarean delivery: restart UFH or LMWH at least 12-18 hrs after delivery.
- Warfarin, LMWH, and UFH do not accumulate in breastmilk thus they can be used in women who breastfeed.
- Estrogen-containing contraceptives should be avoided.

For patients with a personal history of VTE, long-term prophylaxis is indicated and should be coordinated with the patient's primary care physician.

- Thrombophilic patients: Start warfarin 48-72 hours after delivery at a dose of 5 mg daily for 2 days. Continue therapeutic doses of UFH or LMWH for 5 days and until the INR normalized ration is therapeutic (2.0-3.0) for 2 consecutive days.

Inherited Thrombophilia

Inherited thrombophilias have been associated with VTE and adverse pregnancy outcomes. Screening for thrombophilias is controversial and should only be used when the results will affect management decisions. (ACOG, 2013) Testing is **not recommended** for women who have experienced recurrent fetal loss or placental abruption because it is unclear if anticoagulation therapy reduces recurrence. (ACOG, 2013) In addition, screening is not recommended for women with a history of IUGR or pre-eclampsia. Management decisions regarding treatment, thromboprophylaxis, anticoagulant therapy, or antepartum surveillance should be made through an individual risk assessment including: prior history of VTE, inherited thrombophilia, cesarean delivery, immobility, obesity, and family history of VTE. Treatment recommendations are found in Table 1.

Recommendations for screening include:

- Women with a personal history of VTE.
- Women with a first-degree relative (parent or sibling) with a history of thrombophilia.

Ideally, screening tests should be collected at least 6 weeks after a thrombotic event and while the patient is not pregnant or on anticoagulation or hormonal therapy.

If a patient has clinical indications, recommended screening tests include:

- Factor V Leiden mutation
- Prothrombin *G20210A* mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency

Testing for *MTHFR* mutations is no longer recommended. There is insufficient evidence at this time to justify screening for plasminogen activator inhibitor (PAI-1) polymorphisms.

Anticoagulation Therapy

Women with a history of thrombosis or those with an acquired or inherited thrombophilia are candidates for prophylactic or therapeutic anticoagulation therapy during pregnancy and the postpartum period see Table 1. Women who require anticoagulation therapy when they are not pregnant most likely will continue to need treatment during pregnancy. Heparin compounds, unfractionated heparin (UFH) or low molecular weight heparin (LMWH) plus low-dose aspirin, are the preferred anticoagulants for use during pregnancy see Table 2. Neither crosses the placenta and both

are considered safe during pregnancy. (ACOG, 2011 reaffirmed 2014) Warfarin is associated with harmful fetal effects and should not be used in pregnancy unless the woman has a mechanical heart which requires multidisciplinary care. Such woman should be referred to a maternal fetal medicine specialist for care. Women with a prior of thrombosis who have not been evaluated for underlying causes should be tested for antiphospholipid antibodies and inherited thrombophilias.(ACOG, 2011 reaffirmed 2014) The testing results will help guide therapy dosing and monitoring, see Table 1.

Data are conflicting as to whether there is a benefit of adding low-dose aspirin to heparin prophylaxis or therapy in the absence of anti-phospholipid syndrome. However, given the potential increase in the risk of vascular events during pregnancy (e.g. pre-eclampsia or placental dysfunction) for women with a prior VTE, at the University of Alabama at Birmingham (UAB) we typically recommend low-dose aspirin in addition to heparin. Based on the risk-benefit ratio in the US Preventive Service Task Force recommendations, there is no increase in the risk with low–dose aspirin and its addition to the regimen may lower the occurrence of pre-eclampsia and other conditions associated with placental dysfunction.(Areia AL, 2015; de Vries JI, 2012; Henderson JT, 2014)

There are no large clinical trials for preventive treatment of thromboembolism during pregnancy. Recommendations are based on case studies and expert opinion. Acute thromboembolism, DVT or PE, should be treated with anticoagulation therapy using intravenous heparin or subcutaneous LMWH achieving therapeutic doses quickly to prevent clot extension see Table 3. (Peaceman, 2010) Once the patient appears to be hemodynamically stable, she should be transitioned to LMWH for the rest of the pregnancy. Heparin can be monitored to maintain the activated partial thromboplastin time (aPTT) at least 1.5-2 times control throughout the dosing interval or anti-Xa level in the therapeutic range, but since the metabolism of heparin during pregnancy is so rapid, it is difficult to achieve. (Peaceman, 2010) Enoxaparin therapy outside pregnancy is not generally monitored but during pregnancy, adequacy of dosing should be monitored with anti-Factor Xa levels. Target levels vary by laboratory and typically each lab provides a prophylactic target range as well as a therapeutic target range. Dosing of LMWH in patients weighing greater than 100 kg may need adjustment from the standard 1mg/kg recommended dose. This determination should be based on anti-factor Xa levels.

Pneumatic compression devices are recommended in the intrapartum period until ambulatory in women with a known thrombophilia. UFH should also be considered in high risk patients with multiple

comorbid conditions. If the patient is receiving LMWH during pregnancy, she should be switched to a comparable dose of UFH at 36 weeks of gestation to permit neuraxial anesthesia during labor and delivery. (ACOG, 2013) LMWH or UFH can also be discontinued 24-36 hours before labor induction or cesarean section to avoid anticoagulation effect during delivery. Patients receiving anticoagulation therapy should be instructed to discontinue their injections at the onset of labor.

Postpartum doses of UFH should be equal or greater than antepartum therapy. Anticoagulation should not be initiated within 4 hours of epidural removal to reduce the risk of an epidural hematoma. Restart UFH or LMWH at least 6 hours after vaginal delivery or at least 12-18 hours after cesarean. Warfarin can be started 48-72 hours after delivery with an initial dose of 5 mg daily for 2 days while continuing LMWH or UFH for at least 2 days after the INR is therapeutic. Warfarin, LMWH, and UFH do not accumulate in breastmilk thus they can be used in women who breastfeed.

Table 1. Indications and Duration of Outpatient Anticoagulation Use in Pregnancy (adapted from: (ACOG, 2011 reaffirmed 2014, 2013; Areia AL, 2015; Blanchard & Chabetai, 2009; de Vries JI, 2012; Henderson JT, 2014; Nishimura, Otto, & Sorajja, 2014)

Clinical Scenario	Antepartum Management	Postpartum Management
Personal VTE History		
Prior VTE associated with transient risk-factor that is no longer present (excludes a VTE during pregnancy or while on OCPs)	Surveillance without anticoagulation plus/minus low-dose aspirin*	6 weeks PPx LMWH or UFH
Prior single VTE without an associated risk-factor (includes a VTE during a pregnancy or while using an OCP use)	PPx LMWH or UFH Plus/minus low-dose aspirin*	6 weeks PPx LMWH or UFH
Two or more VTEs	Therapeutic LMWH or UFH Plus/minus low-dose aspirin*	6 weeks therapeutic LMWH, UFH, or warfarin
Medical Conditions		
Mechanical heart valve	See below (plus low-dose aspirin)	Return to pre-pregnancy regimen (will need a heparin bridge if transitioning to warfarin)
Atrial fibrillation (active)	Therapeutic LMWH or UFH Plus/minus low-dose aspirin*	6 weeks therapeutic LMWH, UFH, or warfarin
Mitral stenosis (risk of VTE 10-20%)[2]	Therapeutic LMWH or UFH Plus/minus low-dose aspirin*	6 weeks therapeutic LMWH, UFH, or warfarin
Antiphospholipid antibody syndrome without a history of a VTE	PPx LMWH or UFH plus low-dose aspirin	6 weeks PPx LMWH or UFH
Antiphospholipid antibody syndrome with a history of VTE	Therapeutic LMWH or UFH plus low-dose aspirin	6 weeks therapeutic LMWH, UFH, or warfarin
Inherited thrombophilias		
Thrombophilia carrier but no history of VTE		
Low-risk thrombophilia	Surveillance without anticoagulation Plus/minus low-dose aspirin*	Surveillance or 6 weeks PPx LMWH or UFH if additional risk factors exist (obesity, prolonged immobility)

Clinical Scenario	Antepartum Management	Postpartum Management
High-risk thrombophilia	PPx LMWH or UFH Plus/minus low-dose aspirin*	6 weeks PPx LMWH or UFH
Thrombophilia carrier without a personal history of a VTE but a first-degree relative with a h/o a VTE		
Low-risk thrombophilia	Surveillance without anticoagulation plus/minus low-dose aspirin*	6 weeks PPx LMWH or UFH
High-risk thrombophilia	PPx LMWH or UFH Plus/minus low-dose aspirin*	6 weeks PPx LMWH or UFH
Thrombophilia carrier with a history of a single VTE (not on long-term anticoagulation)		
Low-risk thrombophilia	PPx LMWH or UFH Plus/minus low-dose aspirin*	6 weeks PPx LMWH or UFH
High-Risk thrombophilia	Therapeutic LMWH or UFH Plus/minus low-dose aspirin*	6 weeks therapeutic LMWH, UFH, or warfarin
Thrombophilia carrier with a history of 2 prior VTEs	Therapeutic LMWH or UFH Plus/minus low-dose aspirin*	Therapeutic LMWH or UFH Plus/minus low-dose aspirin*

*Data are conflicting as to whether there is a benefit of adding low-dose aspirin to heparin prophylaxis or therapy in the absence of anti-phospholipid syndrome. However, given the potential increase in the risk of vascular events during pregnancy (e.g. pre-eclampsia or placental dysfunction) for women with a prior VTE, at UAB we typically recommend low-dose aspirin in addition to heparin. Based on the risk-benefit ratio in the US Preventive Service Task Force recommendations, there is no increase in the risk with low–dose aspirin and its addition to the regimen may lower the occurrence of pre-eclampsia and other conditions associated with placental dysfunction.

Table 2. Anticoagulant Regimen Definition adapted (ACOG, 2013)

Anticoagulation Regimen	Definition
Prophylactic LMWH*	Enoxaparin, 40 mg SC once daily Dalteparin, 5,000 units SC once daily
Therapeutic LMWH†	Enoxaparin, 1 mg/kg every 12 hours Dalteparin, 200 units/kg once daily Target an anti-Xa level in the therapeutic range for twice daily regimens; slightly higher doses many be needed for once-daily regimen.
Prophylactic UFH	UFH, 5,000-10,000 units SC every 12 hours UFH, 5,000-7,500 units SC every 12 hours in the 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
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) 6 hours after injection; in some patients dosing every 8 hours may be necessary to achieve more sustained therapeutic concentrations.
Postpartum anticoagulation	Prophylactic LMWH/UFH for 6 weeks or warfarin for 6 weeks with a target INR of 2.0-3.0, with initial UFH or LMWH therapy overlap until the INR is 2.0 or more for 2 days

*While anti-Xa monitoring is not routinely recommended for prophylactic regimens, at extremes of body weight especially in patients weighing >100 kg, modification of dose may be required.
†Also referred to as weight adjusted, full treatment dose.

Table 3. Anticoagulation Therapy for DVT or PE adapted (Peaceman, 2010)

Condition	Heparin	Enoxaparin
DVT or PE current pregnancy	IV heparin (aPTT 2-3 times control) for 5-10 days, followed by q 8-12 hour injections to prolong midinterval aPTT 1.5-2 x control for remainder of the pregnancy; anti-Factor Xa levels can alternatively be monitored every 4 hours. Warfarin can be used postpartum.	Enoxaparin 1 mg/kg (100 mg max) q 12 hours; monitor anti-Factor Xa levels at 4-6 hours post injection.

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