THROMBOPHILIAS AND ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN PREGNANCY

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Minnesota Perinatal Physicians
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What is a thrombophilia?

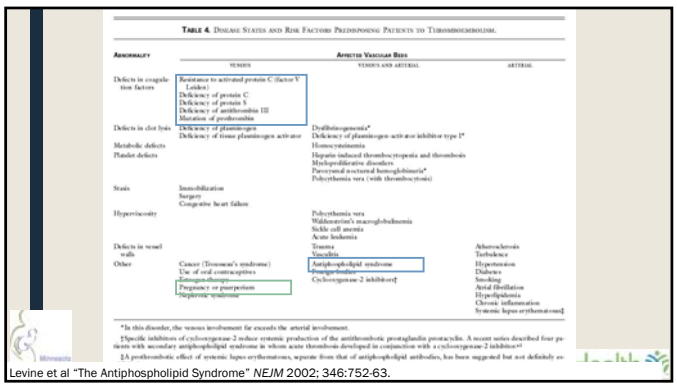


TABLE 4. DISEASE STATES AND RISK FACTORS PREDISPOSING PATIENTS TO THROMBOEMBOLISM.

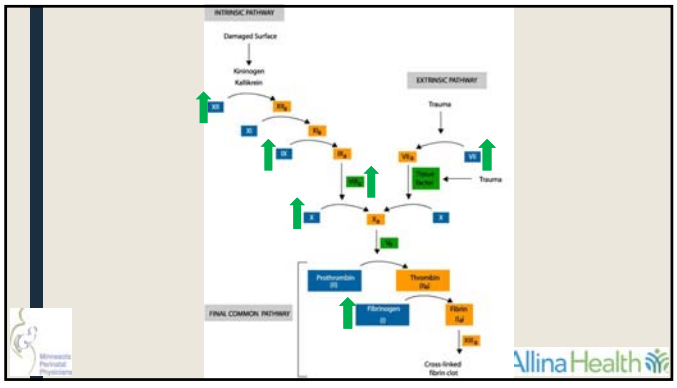
ABNORMALITY	AFFECTED VASCULAR BEDS: VENOUS	VENOUS AND ARTERIAL	ARTERIAL
Defects in coagulation factors	Resistance to activated protein C (factor V Leiden) Deficiency of protein C Deficiency of protein S Deficiency of antithrombin III Mutation of prothrombin		
Defects in clot lysis	Deficiency of plasminogen	Dysfibrinogenemia*	
	Deficiency of tissue plasminogen activator	Deficiency of plasminogen-activator inhibitor type I*	
Metabolic defects		Homocystinemia	
Platelet defects		Heparin-induced thrombocytopenia and thrombosis Myeloproliferative disorders Paroxysmal nocturnal hemoglobinuria* Polycythemia vera (with thrombocytosis)	
Stasis	Immobilization Surgery Congestive heart failure		
Hyperviscosity		Polycythemia vera Waldenström's macroglobulinemia Sickle cell anemia Acute leukemia	
Defects in vessel walls		Trauma Vasculitis	Atherosclerosis Turbulence
Other	Cancer (Trousseau's syndrome) Use of oral contraceptives Estrogen therapy Pregnancy or puerperium Nephrotic syndrome	Antiphospholipid syndrome Oxygen therapy Cyclooxygenase-2 inhibitors†	Hypertension Diabetes Smoking Atrial fibrillation Hyperlipidemia Chronic inflammation Systemic lupus erythematosus‡

*In this disorder, the venous involvement far exceeds the arterial involvement.
†Specific inhibitors of cyclooxygenase-2 reduce systemic production of the antithrombotic prostaglandin prostacyclin. A recent series described four patients with secondary antiphospholipid syndrome in whom acute thrombosis developed in conjunction with a cyclooxygenase-2 inhibitor.[42]
‡A prothrombotic effect of systemic lupus erythematosus, separate from that of antiphospholipid antibodies, has been suggested but not definitely es-

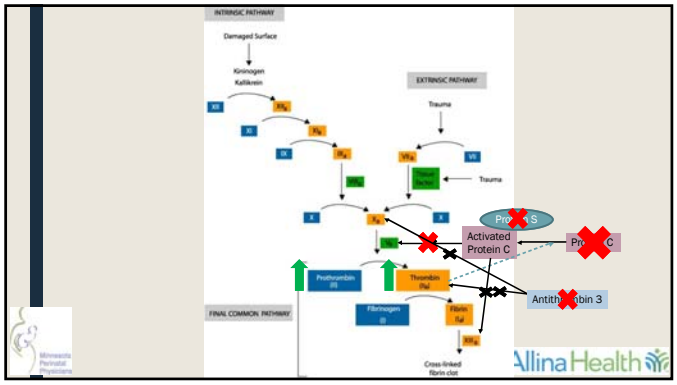
Levine et al "The Antiphospholipid Syndrome" *NEJM* 2002; 346:752-63.

Pregnancy is an inherently thrombophilic state

- Venous thromboembolism complicates 0.5-2.0/1000 pregnancies.
- 9.2% of pregnancy-related deaths.
- 4-5 fold increased risk of VTE compared to nonpregnant women
- Risk persists until 6-12 weeks postpartum

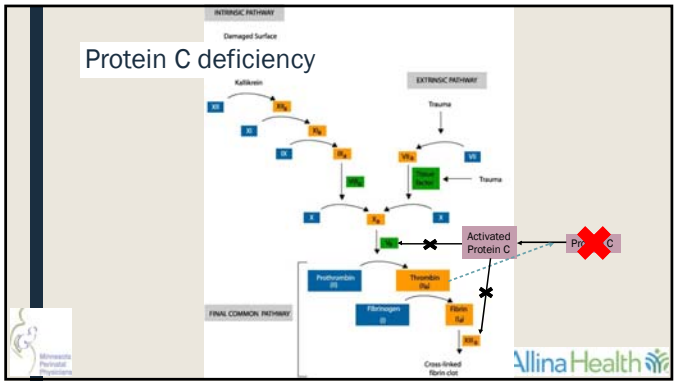


- Inherited thrombophilias
- Acquired thrombophilias (antiphospholipid antibodies)
- Management of patients with thrombophilias



Protein C deficiency

- Multiple mutations in Protein C gene can result in lower levels of Protein C
- Protein C inhibits function of Factor V
- Up to 0.5% of the population may be Protein C resistant
- 0.1-1.7% VTE risk per pregnancy (4-17% if h/o prior VTE)
- Screen with Protein C activity levels (normal >65%)
  - *Abnormal results can be caused by acquired (temporary) protein C resistance → refer to hematology for confirmation*



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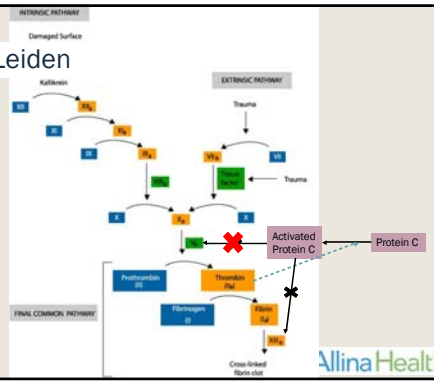
Protein C deficiency

- Screen with Protein C activity levels (normal >65%)
- Heterozygotes for Protein C deficiency usually have levels of 30-65%
- Homozygous RARE, associated with neonatal purpura fulminans
- Also higher risk of Coumadin skin necrosis in heterozygotes

Factor V Leiden

- Activated Protein C Resistance
- Mutation in Factor V gene makes it resistant to inactivation by Protein C
- Most common inherited thrombophilia in the Caucasian population (5% prevalence of Factor V Leiden heterozygous)
  - *Still common in other populations (0.5-2.5%)*
- 0.5-3.1% risk of VTE per pregnancy (10% if h/o prior VTE)
- Screen with genetic test for Factor V leiden gene mutation (not Activated Protein C Resistance test)

Factor V Leiden



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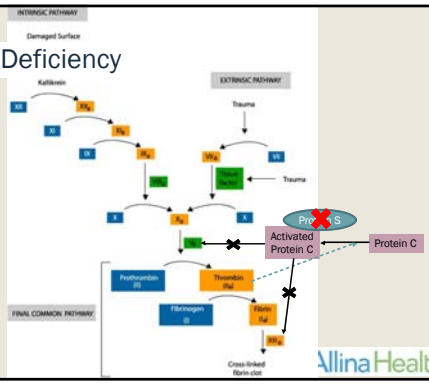
Protein S Deficiency

- Vitamin K dependent protein that serves as a cofactor for activated Protein C
- Free and total protein S levels impacted by age, sex, pregnancy, OCP use, anticoagulation, DIC (among other things)
- Low population prevalence (0.1%)
- 0.3-6.6% risk of VTE per pregnancy (up to 22% if prior VTE)
- Screen with serum Protein S antigen levels (not activity level)
  - *Abnormal <55-60%*
  - *NOT valid in pregnancy (be very suspicious of levels <30%)*

Protein S Deficiency



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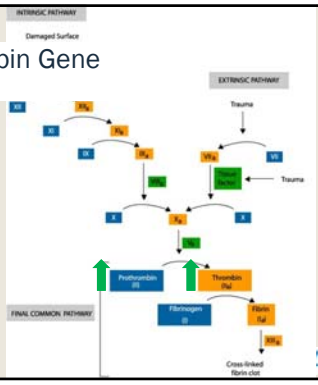
Prothrombin Gene Mutation (G20210A) (Factor 2 Deficiency)

- Mutation in the Prothrombin gene causes elevated levels
- Up to 3% of the population, more common in Caucasian and Latino, less common in African-American and Asian populations
- 1% risk of VTE per pregnancy (10% if history of prior VTE)
- Screen with Prothrombin gene mutation test

Prothrombin Gene Mutation



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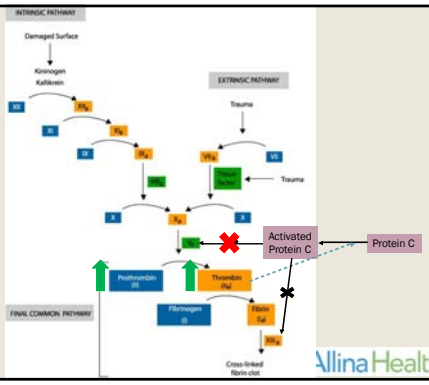
Prothrombin Gene Mutation (G20210A) (Factor 2 Deficiency)

** Combined mutations of Factor V Leiden and Prothrombin Gene Mutation (compound heterozygotes) have a synergistic effect – 4-5% risk of VTE per pregnancy EVEN WITH NO HISTORY **



Antithrombin 3 Deficiency

- Antithrombin 3 inhibits function of Factor Xa and Thrombin
- Various mutations result in decreased antigen or activity levels
- Low population prevalence
- VTE risk depends on specifics of mutation, AT3 levels, family and personal history
  - *As high as 40% during pregnancy in women with strong histories*

Antithrombin 3 Deficiency

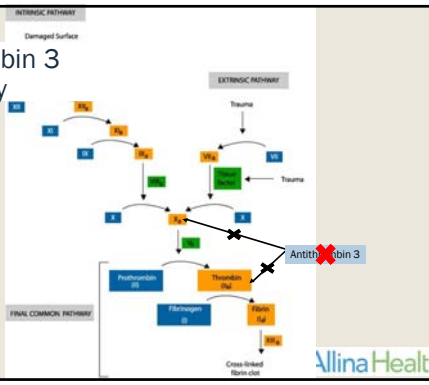


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Table 1. Risk of Venous Thromboembolism With Different Inherited Thrombophilias

	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

Abbreviation: VTE, venous thromboembolism.

Inherited Thrombophilias in Pregnancy. ACOG practice bulletin No. 197. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132: e18-e34.

1. Franco RF, Reitsma PH. Genetic risk factors of venous thrombosis. Hum Genet 2001;109:369–84.
2. Gerhardt A, Scharf RE, Beckmann MW, Struve S, Bender HG, Pilny M, et al. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. N Engl J Med 2000;342:374–80.
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Antiphospholipid antibodies

- A large heterogenous group of antibodies that bind to phospholipids or phospholipid-binding proteins
- Associated with increased risk of venous and arterial thrombosis, poor pregnancy outcomes, thrombocytopenia, thrombotic microangiopathy, stroke, myocardial infarction, valvular abnormalities, hemolytic anemia, renal failure …
- ONLY 3 antiphospholipid antibodies are clinically relevant:
  - *Lupus anticoagulant*
  - *Anti-beta2-glycoprotein 1*
  - *Anticardiolipin*

Miyakis et al, "International Consensus Statement on an Update of the Classification Criteria for Definite Antiphospholipid Antibody Syndrome" *J Thromb Hemostasis* 2006.

Antiphospholipid Antibody Syndrome

- Patients with documented antiphospholipid antibodies who ALSO meet clinical criteria for adverse outcomes resulting from antiphospholipid antibodies
- Must meet BOTH clinical and laboratory criteria

Miyakis et al, "International Consensus Statement on an Update of the Classification Criteria for Definite Antiphospholipid Antibody Syndrome" *J Thromb Hemostasis* 2006.

Antiphospholipid Antibody Syndrome Clinical Criteria

- Thrombosis: one or more clinically significant episodes of thrombosis (venous, arterial or small vessel) in any tissue or organ

AND/OR

- Pregnancy criteria (any of the following):
  - One or more unexplained losses of a morphologically normal fetus after 10 weeks
  - One or more preterm deliveries <34 weeks due to severe pre-eclampsia or IUGR (placental insufficiency)
  - Three or more consecutive unexplained pregnancy losses <10 weeks

Miyakis et al, "International Consensus Statement on an Update of the Classification Criteria for Definite Antiphospholipid Antibody Syndrome" *J Thromb Hemostasis* 2006.

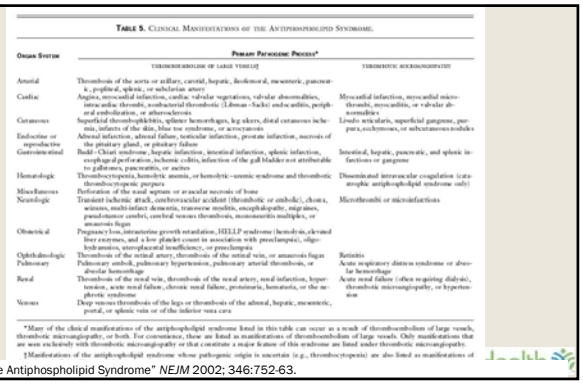


TABLE 5. CLINICAL MANIFESTATIONS OF THE ANTIPHOSPHOLIPID SYNDROME.

ORGAN SYSTEM	PRIMARY PATHOGENIC PROCESS*	
	THROMBOEMBOLISM OF LARGE VESSELS†	THROMBOTIC MICROANGIOPATHY
Arterial	Thrombosis of the aorta or axillary, carotid, hepatic, iliofemoral, mesenteric, pancreatic, popliteal, splenic, or subclavian artery	
Cardiac	Angina, myocardial infarction, cardiac valvular vegetations, valvular abnormalities, intracardiac thrombi, nonbacterial thrombotic (Libman–Sacks) endocarditis, peripheral embolization, or atherosclerosis	Myocardial infarction, myocardial microthrombi, myocarditis, or valvular abnormalities
Cutaneous	Superficial thrombophlebitis, splinter hemorrhages, leg ulcers, distal cutaneous ischemia, infarcts of the skin, blue toe syndrome, or acrocyanosis	Livedo reticularis, superficial gangrene, purpura, ecchymoses, or subcutaneous nodules
Endocrine or reproductive	Adrenal infarction, adrenal failure, testicular infarction, prostate infarction, necrosis of the pituitary gland, or pituitary failure	
Gastrointestinal	Budd–Chiari syndrome, hepatic infarction, intestinal infarction, splenic infarction, esophageal perforation, ischemic colitis, infarction of the gall bladder not attributable to gallstones, pancreatitis, or ascites	Intestinal, hepatic, pancreatic, and splenic infarctions or gangrene
Hematologic	Thrombocytopenia, hemolytic anemia, or hemolytic–uremic syndrome and thrombotic thrombocytopenic purpura	Disseminated intravascular coagulation (catastrophic antiphospholipid syndrome only)
Miscellaneous	Perforation of the nasal septum or avascular necrosis of bone	
Neurologic	Transient ischemic attack, cerebrovascular accident (thrombotic or embolic), chorea, seizures, multi-infarct dementia, transverse myelitis, encephalopathy, migraines, pseudotumor cerebri, cerebral venous thrombosis, mononeuritis multiplex, or amaurosis fugax	Microthrombi or microinfarctions
Obstetrical	Pregnancy loss, intrauterine growth retardation, HELLP syndrome (hemolysis, elevated liver enzymes, and a low platelet count in association with preeclampsia), oligohydramnios, uteroplacental insufficiency, or preeclampsia	
Ophthalmologic	Thrombosis of the retinal artery, thrombosis of the retinal vein, or amaurosis fugax	Retinitis
Pulmonary	Pulmonary emboli, pulmonary hypertension, pulmonary arterial thrombosis, or alveolar hemorrhage	Acute respiratory distress syndrome or alveolar hemorrhage
Renal	Thrombosis of the renal vein, thrombosis of the renal artery, renal infarction, hypertension, acute renal failure, chronic renal failure, proteinuria, hematuria, or the nephrotic syndrome	Acute renal failure (often requiring dialysis), thrombotic microangiopathy, or hypertension
Venous	Deep venous thrombosis of the legs or thrombosis of the adrenal, hepatic, mesenteric, portal, or splenic vein or of the inferior vena cava	

*Many of the clinical manifestations of the antiphospholipid syndrome listed in this table can occur as a result of thromboembolism of large vessels, thrombotic microangiopathy, or both. For convenience, those are listed as manifestations of thromboembolism of large vessels. Only manifestations that are seen exclusively with thrombotic microangiopathy or that constitute a major feature of this syndrome are listed under thrombotic microangiopathy.

†Manifestations of the antiphospholipid syndrome whose pathogenic origin is uncertain (e.g., thrombocytopenia) are also listed as manifestations of

Levine et al "The Antiphospholipid Syndrome" *NEJM* 2002; 346:752-63.

Antiphospholipid Antibody Syndrome Laboratory Criteria

One or more of:

- *Lupus anticoagulant*
- *Anti-beta2-glycoprotein 1 IgG or IgM at high titer (>99th percentile by reporting laboratory)*
- *Anticardiolipin IgG or IgM at medium or high titer (>40)*

Positive on TWO occasions >12 weeks apart

Miyakis et al, "International Consensus Statement on an Update of the Classification Criteria for Definite Antiphospholipid Antibody Syndrome" *J Thromb Hemostasis* 2006.

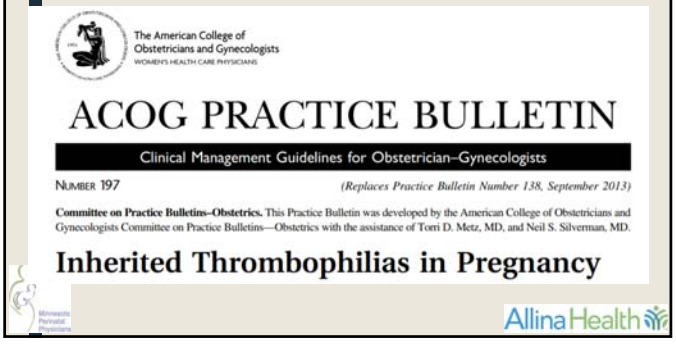
Antiphospholipid Antibody Syndrome Management in Pregnancy

- Aspirin 81mg daily PLUS prophylactic Heparin or Lovenox
  - *Decreases risk of pregnancy loss by 50%*
  - *Decreases risk of thrombotic event*
- NO additional benefit from corticosteroids or IVIG
- Growth US, antenatal testing, surveillance for pre-eclampsia due to elevated risk of adverse pregnancy outcomes
- Continue anticoagulation for 6 weeks postpartum

Antiphospholipid Syndrome. ACOG practice bulletin No. 132. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120: 1514-21.

Management of patients with thrombophilias

- Who should we test for thrombophilias?
- How should we test for thrombophilias?
- Which patients need anticoagulation?
  - *Which anticoagulants?*
  - *How much anticoagulation?*
  - *What about around the time of delivery?*
  - *What about the postpartum period?*
  - *What about breastfeeding?*



The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 197 *(Replaces Practice Bulletin Number 138, September 2013)*

Committee on Practice Bulletins–Obstetrics. This Practice Bulletin was developed by the American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics with the assistance of Torri D. Metz, MD, and Neil S. Silverman, MD.

Inherited Thrombophilias in Pregnancy

WHO should we test for thrombophilias?

- Prior venous thromboembolism?
  - *Inherited thrombophilias + antiphospholipid antibodies*
- Family history of inherited thrombophilia?
  - *Test only for known thrombophlilia or only inherited thrombophlilia (if specific mutation unknown)*
- History of stillbirth/Severe IUGR/early pre-eclampsia/other adverse pregnancy outcomes?
  - *Antiphospholipid antibodies ONLY*
- Recurrent pregnancy loss?
  - *Antiphospholipid antibodies ONLY*

WHO should we test for thrombophilias?

- Association between inherited thrombophilias and pregnancy complications:
  - *Most studies small and retrospective*
  - *Larger studies find no (or very weak) associations*
- Anticoagulation NOT shown to improve pregnancy outcomes in women with thrombophilias
- ACOG does not recommend inherited thrombophilia evaluation for history of pregnancy complications alone
- ASRM does not recommend inherited thrombophilia evaluation for history of recurrent pregnancy loss

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HOW should we test for thrombophilias?

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	resistance assay (second generation)			
	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*	*Not valid on OCPs either	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.

Inherited Thrombophilias in Pregnancy. ACOG practice bulletin No. 197. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132: e18-e34.

HOW should we test for thrombophilias: Antiphospholipid Antibodies

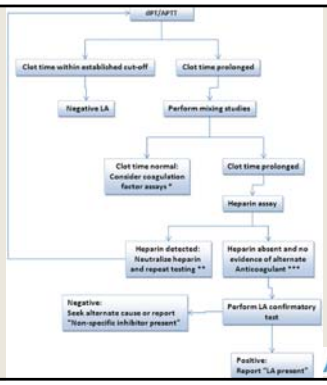
- Lupus anticoagulant*
- Anti-beta2-glycoprotein 1 IgG and IgM**
- Anticardiolipin IgG and IgM

Don't forget to repeat testing 12 weeks later if positive!

*Lupus anticoagulant testing less reliable on anticoagulation

**Some labs will send IgA as well (not clinically relevant)

Miyakis et al, "International Consensus Statement on an Update of the Classification Criteria for Definite Antiphospholipid Antibody Syndrome" *J Thromb Hemostasis* 2006.



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A Special Note about MTHFR…

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A Special Note about MTHFR…

- No evidence that MTHFR increases thrombosis risk in pregnancy
- No evidence that MTHFR increases pregnancy complications


ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing

Evaluation and treatment of recurrent pregnancy loss: a committee opinion

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

Inherited Thrombophilias in Pregnancy

Your pregnant patient has a thrombophilia – NOW WHAT? (Which patients need anticoagulation?

- ALL patients with antiphospholipid antibody SYNDROME
- ALL patients with high risk thrombophilias
- Some patients with low risk thrombophilias

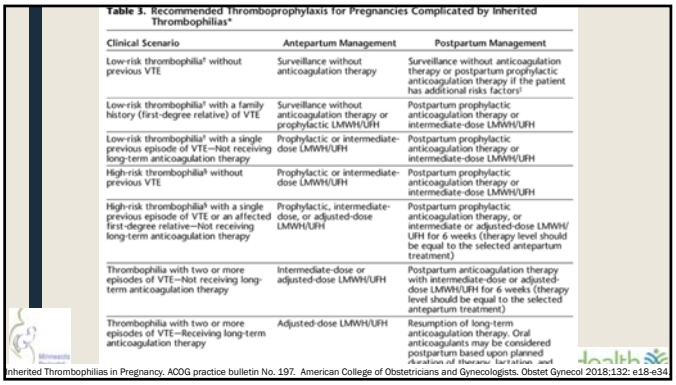
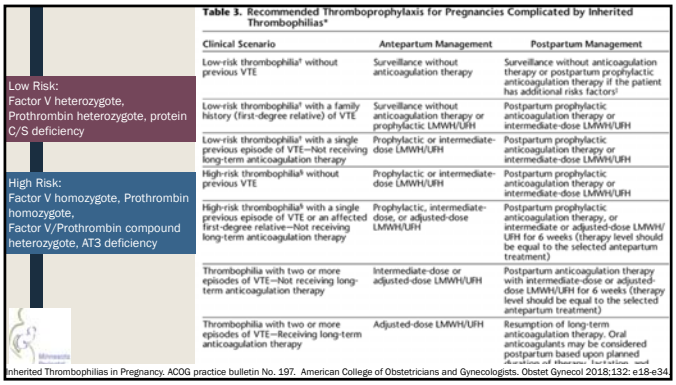


Table 3. Recommended Thromboprophylaxis for Pregnancies Complicated by Inherited Thrombophilias*

Clinical Scenario	Antepartum Management	Postpartum Management
Low-risk thrombophilia† without previous VTE	Surveillance without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risks factors‡
Low-risk thrombophilia† with a family history (first-degree relative) of VTE	Surveillance without anticoagulation therapy or prophylactic LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
Low-risk thrombophilia† with a single previous episode of VTE—Not receiving long-term anticoagulation therapy	Prophylactic or intermediate-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ without previous VTE	Prophylactic or intermediate-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ with a single previous episode of VTE or an affected first-degree relative—Not receiving long-term anticoagulation therapy	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy, or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)
Thrombophilia with two or more episodes of VTE—Not receiving long-term anticoagulation therapy	Intermediate-dose or adjusted-dose LMWH/UFH	Postpartum anticoagulation therapy with intermediate-dose or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)
Thrombophilia with two or more episodes of VTE—Receiving long-term anticoagulation therapy	Adjusted-dose LMWH/UFH	Resumption of long-term anticoagulation therapy. Oral anticoagulants may be considered postpartum based upon planned

Inherited Thrombophilias in Pregnancy. ACOG practice bulletin No. 197. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132: e18-e34.


Low Risk:
Factor V heterozygote, Prothrombin heterozygote, protein C/S deficiency

High Risk:
Factor V homozygote, Prothrombin homozygote, Factor V/Prothrombin compound heterozygote, AT3 deficiency

Table 3. Recommended Thromboprophylaxis for Pregnancies Complicated by Inherited Thrombophilias*

Clinical Scenario	Antepartum Management	Postpartum Management
Low-risk thrombophilia† without previous VTE	Surveillance without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risks factors‡
Low-risk thrombophilia† with a family history (first-degree relative) of VTE	Surveillance without anticoagulation therapy or prophylactic LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
Low-risk thrombophilia† with a single previous episode of VTE—Not receiving long-term anticoagulation therapy	Prophylactic or intermediate-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ without previous VTE	Prophylactic or intermediate-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ with a single previous episode of VTE or an affected first-degree relative—Not receiving long-term anticoagulation therapy	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy, or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)
Thrombophilia with two or more episodes of VTE—Not receiving long-term anticoagulation therapy	Intermediate-dose or adjusted-dose LMWH/UFH	Postpartum anticoagulation therapy with intermediate-dose or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)
Thrombophilia with two or more episodes of VTE—Receiving long-term anticoagulation therapy	Adjusted-dose LMWH/UFH	Resumption of long-term anticoagulation therapy. Oral anticoagulants may be considered postpartum based upon planned

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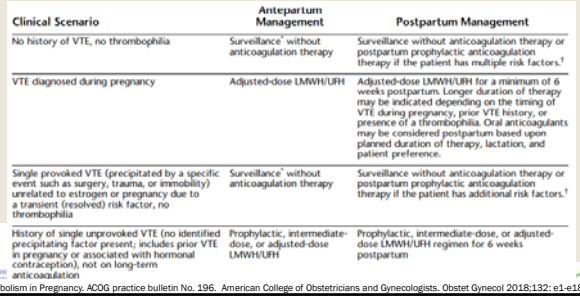
A side note … some patients WITHOUT thrombophilia still qualify for anticoagulation


Clinical Scenario	Antepartum Management	Postpartum Management
No history of VTE, no thrombophilia	Surveillance without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has multiple risk factors.†
VTE diagnosed during pregnancy	Adjusted-dose LMWH/UFH	Adjusted-dose LMWH/UFH for a minimum of 6 weeks postpartum. Longer duration of therapy may be indicated depending on the timing of VTE during pregnancy, prior VTE history, or presence of a thrombophilia. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.
Single provoked VTE (precipitated by a specific event such as surgery, trauma, or immobility) unrelated to estrogen or pregnancy due to a transient (resolved) risk factor, no thrombophilia	Surveillance without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risk factors.†
History of single unprovoked VTE (no identified precipitating factor present; includes prior VTE in pregnancy or associated with hormonal contraception), not on long-term anticoagulation	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH regimen for 6 weeks postpartum

Thromboembolism in Pregnancy. ACOG practice bulletin No. 196. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132: e1-e18.

Your pregnant patient qualifies for anticoagulation!

- Which patients need anticoagulation?
  - *What type of anticoagulation?*
  - *How much anticoagulation?*
  - *What about around the time of delivery?*
  - *What about the postpartum period?*
  - *What about breastfeeding?*

Your pregnant patient qualifies for anticoagulation!

- Heparin and Lovenox (LMWH) bind to antithrombin 3 and activate it.
  - *Heparin causes inhibition of Xa, IIa, iXa, XXIa, XXIIa*
  - *LMWH causes a more specific effect on factor Xa*
- Duration of action: Heparin 4-12 hours, Lovenox 12-24 hours
- Administration: Heparin IV or SC, Lovenox SC

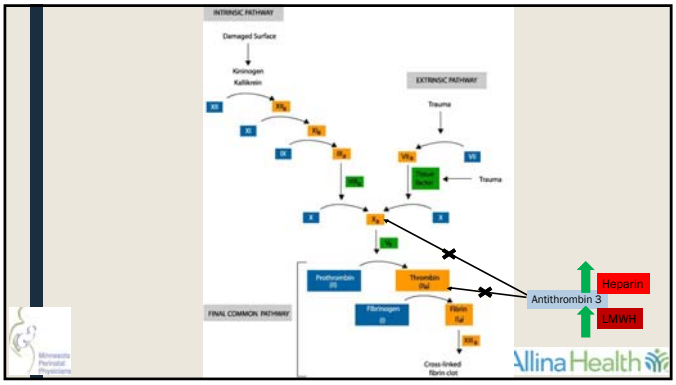


Table 4. Anticoagulation Regimen Definitions

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 0.6–1.0 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 × control) 6 hours after injection

1.5mg/kg q24h NOT appropriate in pregnancy

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Check anti-Xa level once each trimester

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Usually need q8h dosing for therapeutic SC heparin

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Anticoagulation management intrapartum/postpartum

- Criteria for regional anesthesia: 12 hours after last heparin dose, 24 hours after last lovenox dose (usually)
- Consider transition from lovenox to heparin at 36 weeks, or sooner if concern for preterm delivery
  - *May not be ideal for women on therapeutic regimens*
- Consider IOL at 39-40 weeks to facilitate holding anticoagulation
- Restart anticoagulation 6-12 hours after delivery
  - *If concern for hemorrhage in a patient on therapeutic dosing, can start prophylactic dosing at 6-12 hours and switch to therapeutic dosing at 24 hours*
- Continue for 6 weeks postpartum

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Other anticoagulants …

- Coumadin – vitamin K antagonist
  - *Blocks action of vitamin K dependent clotting factors*
  - *Initial PRO-thrombotic action (inhibition of protein C/S) then antithrombotic action*
  - *Associated with Warfarin Embryopathy (facial dysmorphism, skeletal abnormalities, developmental delay, IUGR)*
  - *Causes fetal anticoagulation as well as maternal*
  - *Occasionally used in pregnancy for very high risk patients (artificial heart valves)*
- NOACs (Novel Oral Anticoagulants) – Xarelto, Pradaxa, Elequis
  - *Direct thrombin inhibitors or Factor Xa inhibitors*
  - *Limited pregnancy safety data, concern for increased risk of miscarriage and hemorrhage*

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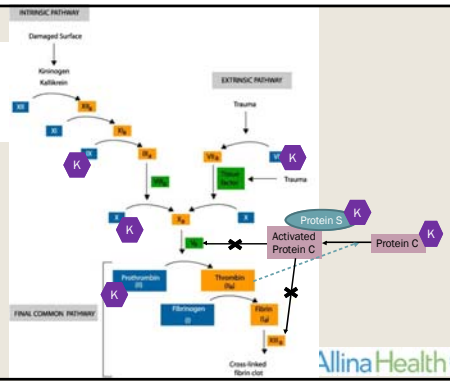
Vitamin K dependent clotting factors



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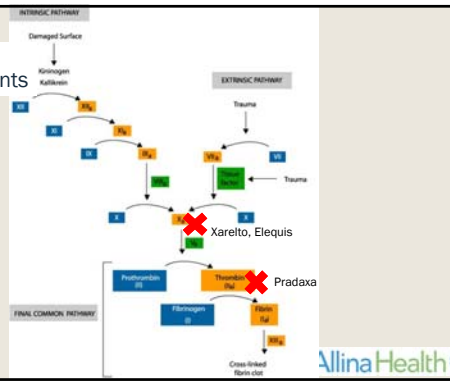
Novel oral anticoagulants



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Breastfeeding and anticoagulation

- Heparin, Lovenox, Coumadin all found in very low levels in breastmilk
  - *Safe for breastfeeding*
- Avoid NOACs due to lack of data
  - *If a patient is determined to breastfeed on NOAC, contact InfantRisk (Texas Tech) who maintain a safety registry*

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Example patient A – personal history of DVT while on OCPs

- Do we test for thrombophilias?
- Do we anticoagulate?
- Antepartum dosing?
- Transition to Heparin?
- Postpartum plan?

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Example patient B – Family history of father with 2 DVTs, died of PE, patient told that her father's blood was "too thick" but never knew why. Patient has personal history of DVT after knee surgery.

- Do we test for thrombophilias? – YES – ANTITHROMBIN 3 levels LOW
- Do we anticoagulate?
- Antepartum dosing?
- Transition to Heparin?
- Postpartum plan?

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Example patient C – Family history of mother with DVT, mother tested positive for Factor V Leiden

- Do we test for thrombophilias? – YES – positive for Factor V Leiden heterozygote
- Do we anticoagulate?
- Antepartum dosing?
- Transition to Heparin?
- Postpartum plan?

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