Maine Medical PARTNERS Women's Health

*A department of Maine Medical Center*

# Inherited Thrombophilias in Pregnancy

## Background:

Inherited thrombophilias are significant contributors to venous thromboembolism (VTE) associated with pregnancy. Current data suggest that inherited thrombophilias do not appear to be associated with increased risks of fetal loss, pre-eclampsia, or fetal growth restriction, although an association with placental abruption remains uncertain.

## Most common disorders:

1. Antithrombin III (AT III) deficiency
2. Protein C (PC) deficiency
3. Protein S (PS) deficiency
4. Activated protein C resistance (APCR) due to Factor V Leiden mutation (Factor V Leiden)
5. Mutation in prothrombin gene (Prothrombin G20210A)
6. Hyperhomocysteinemia

   Note: Testing for MTHFR mutations is not recommended as part of VTE evaluation.

These inherited coagulopathies, with the exception of hyperhomocysteinemia, are responsible for increased risks of VTE.

## Effects of pregnancy:

- A 20% increase in levels of fibrinogen, factors II, VII, X, VIII and XII.
- Endogenous anticoagulant levels increase minimally (TFPI, α – 2 – Macroglobulin).
- ATIII, heparin co factor II and protein C remain constant.
- Protein S significantly decreases.
- Factor VIII levels are elevated.

The net effect of these pregnancy induced hemostatic changes is to promote clot formation.

## Factor V Leiden Mutation (FVL):

- Prevalence
  - 5% of European population.
  - 3% of African American whose ancestors are not recent immigrants are heterozygous for FVL.
- 40% of VTE in pregnancy occurs in pregnant patients heterozygous for FVL.
- Risks of VTE (see Table 1 below).

Prothrombin Gene G20210A:

- Present in 3% of European population.
- 17% of VTE in pregnancy occur in association with prothrombin gene mutation.
- Risks of VTE (see Table 1 below).

Protein C Deficiency:

- Prevalence
  - 0.2-0.3% by functional assay.
- Results from > 160 distinct mutations.
- Risks for VTE (see Table 1 below).

Protein S Deficiency:

- Caused by either silenced gene or mutation causing low protein S levels and activity.
- Assays affected by pregnancy.
  - Cutoff for free protein S antigen level in 2nd trimester is 30%.
  - Cutoff for free protein S antigen level in 3rd trimester is 24%.
- Risks of VTE (see Table 1 below).

Antithrombin III Deficiency:

- Rarest and most thrombogenic thrombophilia.
- Results from > 250 mutations causing reduced antigen level and activity or normal antigen level with reduced activity.
- Prevalence
  - 1/2500
- Risks of VTE (see Table 1 below).

Methylenetetrahydrofolate Reductase Mutations (MTHFR):

- Homozygosity most common cause of hyperhomocysteinemia.
- Prevalence
  - C677T and A1298C present in 10-16% and 4-6% of all Europeans, respectively.
- Mutations alone do not raise risk of VTE and elevated homocysteine levels are only weak VTE risk factors.
- Testing for MTHFR mutations is not recommended as part of VTE evaluation.

**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.

## Management Issues

### Who should be tested?

- Personal history of VTE with non-recurrent risk factor.
- First-degree relative with high-risk thrombophilia.
- Recurrent pregnancy loss or placental abruption are **not** indications for testing.

### How to test patients:

**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.

Who should be treated and how?:

- Decision to treat with thromboprophylaxis, anticoagulant therapy, or surveillance is influenced by VTE history, thrombophilia severity, and other risk factors.
- Management should be individualized.
- Postpartum treatment should at least equal antepartum treatment.
- Warfarin and Low Molecular Weight Heparin (LMWH) are compatible with breast feeding.
- Consider pneumatic compression boots or elastic stockings in patients with known thrombophilia until ambulatory postpartum.
- Consider substituting unfractionated heparin (UFH) for LMWH at 36 weeks, sooner if earlier delivery is anticipated.
- Instruct patients to withhold injections at onset of labor.
- Regional anesthesia need not be withheld beyond 12 hours of prophylactic or 24 hours after a therapeutic dose of LMWH.
- If rapid reversal of UFH or LMWH is needed, protamine sulfate can be used.
- Postpartum UFH or LMWH can be started 4-6 hours after vaginal delivery and 6-12 hours after cesarean delivery.
- UFH or LMWH should be continued for at least 3-5 days after initiating warfarin in patients undergoing such treatment or until international normalized ratio (INR) is therapeutic for 2 consecutive days.
- Avoid estrogen-containing contraception.

**Table 3.** Recommended Pharmacologic Thromboprophylaxis in Pregnancy and the Postpartum Period

| 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 |
| 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 anti-coagulation 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 anti-coagulation 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) |
| Two or more episodes of VTE—Not receiving long-term anticoagulation therapy (regardless of thrombophilia) | 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) |
| Two or more episodes of VTE—Receiving long-term anticoagulation therapy (regardless of thrombophilia) | Adjusted-dose LMWH or UFH | Resumption of long-term anticoagulation therapy. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference. |

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

*VTE risk assessment should be performed prepregnancy or early in pregnancy and repeated if complications develop, particularly those necessitating hospitalization or prolonged immobility.

†First-degree relative with a history of a thrombotic episode, or other major thrombotic risk factors (eg, obesity, prolonged immobility, cesarean delivery).

‡Low-risk thrombophilia: Factor V Leiden heterozygote; prothrombin G20210A mutation heterozygote; protein C or protein S deficiency, antiphospholipid antibody.

§High-risk thrombophilias include Factor V Leiden homozygosity, prothrombin gene G20210A mutation homozygosity, heterozygosity for factor V Leiden and prothrombin G20210A mutation, or antithrombin deficiency.

**Table 4.** Anticoagulation Regimen Definitions

| Anticoagulation Regimen | Anticoagulation Dosage |
|---|---|
| Prophylactic LMWH* | Enoxaparin, 40 mg SC once daily<br>Dalteparin, 5,000 units SC once daily<br>Tinzaparin, 4,500 units SC once daily<br>Nadroparin 2,850 units SC once daily |
| Intermediate-dose LMWH | Enoxaparin 40 mg SC every 12 hours<br>Dalteparin 5,000 units SC every 12 hours |
| Adjusted-dose (therapeutic) LMWH† | Enoxaparin, 1 mg/kg every 12 hours<br>Dalteparin, 200 units/kg once daily<br>Tinzaparin, 175 units/kg once daily<br>Dalteparin, 100 units/kg every 12 hours<br>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<br>UFH, 7,500–10,000 units SC every 12 hours in the second trimester<br>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 |
| 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.

**Table 4.** Timing of Neuraxial Anesthesia in Relation to Pharmacologic Anticoagulation

| Dosage Regimen | Intrapartum, Elective Procedure | Intrapartum, Urgent/Emergent Procedure | Postpartum |
|---|---|---|---|
| UFH prophylaxis (7,500 units SC twice daily or 10,000 units SC twice daily) | Hold dose for 12 hours and assess coagulation status before administering neuraxial anesthesia | Hold dose for 12 hours and assess coagulation status before administering neuraxial anesthesia. However, in urgent cases with greater competing risks from general anesthesia, placement of neuraxial anesthesia may be appropriate | Wait at least 1 hour after neuraxial blockade and catheter removal before restarting heparin |
| UFH adjusted-dose (>10,000 units per dose or >20,000 units per day) | Hold dose for 24 hours and assess coagulation status before administering neuraxial anesthesia | If at least 24 hours since last dose and aPTT within normal limits or undetectable anti-Xa, likely low risk for neuraxial blockade | Wait at least 1 hour after neuraxial blockade or catheter removal before restarting heparin |
| Low-dose LMWH prophylaxis | Wait 12 hours after last dose before neuraxial blockade | Insufficient data to make a recommendation for placement of neuraxial blockade less than 12 hours from last dose of LMWH. In high risk situations in which intervention is needed, risks of general anesthesia may outweigh risks of spinal epidural hematoma | Wait at least 12 hours after neuraxial blockade and at least 4 hours after catheter removal to restart LMWH prophylaxis |
| LMWH intermediate-dose or adjusted-dose | Wait 24 hours after last dose before neuraxial blockade | If less than 24 hours, insufficient evidence to recommend proceeding with neuraxial blockade | Consider waiting at least 24 hours after neuraxial blockade *and* at least 4 hours after catheter removal to restart LMWH anticoagulation |

Abbreviations: LMWH, low-molecular-weight heparin; SC, subcutaneously; UFH, unfractionated heparin.

## Notes

### Calcium hemostasis

Because of the osteopenic effects of heparin, calcium supplementation should be considered (1500 mg qd) as well as weight bearing exercise following the pregnancy.

Bone densitometry could be considered in patients receiving over 15,000 U for greater than 6 months.

### References:

Inherited thrombophilias in pregnancy. ACOG Practice Bulletin No. 197. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e18-34.

Thromboembolism in pregnancy. ACOG Practice Bulletin No. 196. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e1-17.