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)*

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Inherited Thrombophilias in Pregnancy

Inherited thrombophilias are associated with an increased risk of venous thromboembolism and have been linked to adverse outcomes in pregnancy. However, there is limited evidence to guide screening for and management of these conditions in pregnancy. The purpose of this document is to review common thrombophilias and their association with maternal venous thromboembolism risk and adverse pregnancy outcomes, indications for screening to detect these conditions, and management options in pregnancy. This Practice Bulletin has been revised to provide additional information on recommendations for candidates for thrombophilia evaluation, updated consensus guidelines regarding the need for prophylaxis in women with an inherited thrombophilia during pregnancy and the postpartum period, and discussion of new published consensus guidelines from the Society for Obstetric Anesthesia and Perinatology addressing thromboprophylaxis and neuraxial anesthetic considerations in the obstetric population.

Background

The Hemostatic Paradox of Pregnancy

Pregnancy poses a particularly complex hemostatic challenge. Successful pregnancy requires the avoidance of hemorrhage during implantation and endovascular cytotrophoblast remodeling of maternal spiral arteries. Maintaining hemostatic balance during pregnancy requires alterations in local uterine and systemic clotting, as well as anticoagulant and fibrinolytic proteins. The decidual layer of the uterus plays a crucial role in the prevention of hemorrhage during implantation, placentation, and the third stage of labor (1, 2). Confirmation of the crucial role that the decidua plays in hemostasis is demonstrated by hemorrhage associated with obstetric conditions marked by absent or impaired decidua (eg, ectopic pregnancy and placenta accreta). Conversely, decidual tissue factor also can promote the intense hypofibrinogenemia and disseminated intravascular coagulation observed in decidual hemorrhage (ie, placental abruption).

Normal pregnancy physiology is marked by increased clotting potential, decreased anticoagulant activity, and decreased fibrinolysis (3–5). The thrombotic potential of pregnancy is exacerbated by venous stasis in the lower extremities due to compression of the inferior vena cava and pelvic veins by the enlarging uterus, a hormone-mediated increase in venous capacitance, insulin resistance, and hyperlipidemia. These factors contribute to the fact that venous thromboembolism (VTE) complicates approximately 0.5–2.0 per 1,000 pregnancies, and contributes to 9.2% of pregnancy-related deaths in the United States (6–12).

Women who are pregnant or in the postpartum period have a fourfold to fivefold increased risk of thromboembolism compared with nonpregnant women (13, 14). The risk of recurrent VTE is increased threefold to fourfold (relative risk [RR], 3.5; 95% CI 1.6–7.8) in pregnant women compared with nonpregnant women, with a recurrence rate of 10.9% per patient–year during pregnancy (15). Inherited thrombophilias are associated with increased risk of VTE (Table 1), which makes detection of these mutations a logical target for prevention of the morbidity and mortality of VTE in the peripartum period. However, it is controversial whether there is an association between inherited thrombophilias and uteroplacental thrombosis that leads to adverse pregnancy outcomes such as fetal loss, preeclampsia, fetal growth restriction, and placental abruption (16).

This possible association has resulted in increased screening for thrombophilias in pregnancy, including detection in extended carrier panels frequently obtained before or during pregnancy, despite the fact that empiric treatment of identified thrombophilia carriers during pregnancy has not been confirmed to confer any discrete benefit regarding pregnancy outcomes, other than thromboembolism prevention in at-risk women.

Prevalence of Common Inherited Thrombophilias

Factor V Leiden

The prevalence of the factor V Leiden mutation in European populations is approximately 5% (17, 18). In a survey of 4,047 American men and women participating in two longitudinal prospective studies, carrier

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.

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frequencies of factor V Leiden mutation in different racial and ethnic groups were as follows: Caucasians (5.27%; 95% CI 4.42–6.22%), Hispanic Americans (2.21%), African Americans (1.23%), Asian Americans (0.45%), and Native Americans (1.25%) (17).

The mutation renders factor V Leiden refractory to proteolysis by activated protein C. Women who are heterozygous for factor V Leiden have been observed to account for approximately 40% of cases of VTE during pregnancy. Although the risk of VTE among pregnant women who are heterozygous for factor V Leiden without a personal history of VTE or an affected first-degree relative with a thrombotic episode before age 50 years is increased above the baseline pregnancy risk, it is estimated to be no more than 5–12/1,000 deliveries (19–21). In contrast, this risk increases to up to 10% among pregnant women heterozygous for the factor V Leiden mutation with a personal history of VTE (20–22). A woman who is heterozygous for factor V Leiden with only an affected first-degree relative but with no personal history of VTE only has a slightly higher risk of VTE during pregnancy (15/1,000 deliveries) than that conferred by her thrombophilia alone (20, 21). Pregnant women who are homozygous for factor V Leiden without a personal history of VTE or an affected first-degree relative have a 1–2% risk for VTE, whereas those with such a history have a 17% risk (20).

Prothrombin G20210A

The prothrombin G20210A mutation is a point mutation that results in elevated circulating prothrombin levels (18). The prothrombin G20210A mutation is present in approximately 3% of the European population, and it has been reported to account for 17% of cases of VTE in pregnancy (19). In a systematic review, North Americans were noted to have a prevalence of prothrombin gene mutation of 3.6% in Caucasians, 3.5% in Hispanics, 0–1.7% in African Americans, and 0–0.6% in American Indians (23). The carrier rate in this study was 0% for Asians living in Japan, Singapore, China, Oman, South Korea, and India (23).

As with factor V Leiden, a personal history of VTE increases the risk of VTE in pregnancy for carriers of the prothrombin gene mutation. Without such a history, heterozygous carriers of the prothrombin G20210A mutation have a less than 1% risk of VTE during pregnancy. For a carrier with a personal history of VTE, the risk increases to at least 10% (19, 21). Also, as with factor V Leiden, heterozygous prothrombin gene mutation carriers without a personal history of VTE have only a slight increase in risk during pregnancy if an affected first-degree relative exists (21). Pregnant women who are homozygous for the prothrombin G20210A mutation without a personal or positive family history have a 2–3% increased risk of VTE in pregnancy. The combination of factor V Leiden and prothrombin G20210A mutations has synergistic hypercoagulable effects. Although present in only 1 per 10,000 patients, women who are heterozygous for factor V Leiden and prothrombin G20210A mutations have a 4–5% risk of VTE even without a personal or positive family history (19, 20).

Protein C Deficiency

Protein C deficiency has been linked to more than 160 distinct mutations that produce a highly variable phenotype (18). Levels of protein C vary even among individuals with known familial mutations (24), which results in a lack of clarity regarding an appropriate lower limit of normal for protein C levels. The prevalence of protein C deficiency is dependent on the cutoff used. In one study, protein C levels of 31–51% were found in 0.2% of blood donors; all of these individuals were heterozygous for protein C gene mutations (25). However, many laboratories consider a result of less than 65% to be abnormal (26). Protein C levels of 55–65% were found in 1.5% of blood donors consistent with either heterozygosity for a gene mutation or low normal results (25). Consultation with a hematologist may be helpful in interpreting an abnormal protein C result.

The risk of VTE in pregnancy among typical protein C deficient patients with a personal or family history of VTE has been reported to be 2–8% (27–29). In pooled estimates, the absolute risk of pregnancy-related VTE in women with protein C deficiency and no family history is 0.7% (95% CI 0.3–1.5%) (21). The absolute risk increases to an estimated 1.7% (95% CI 0.4–8.9%) in familial studies with a confirmed proband with protein C deficiency and symptomatic VTE (21). Differences in the prevalence of protein C deficiency by racial or ethnic group are not delineated. Although rare, newborns who are homozygous for protein C deficiency may develop neonatal purpura fulminans, a rare life-threatening condition characterized by disseminated intravascular coagulation and hemorrhagic skin necrosis, and will require lifetime anticoagulation therapy (30).

Protein S Deficiency

Protein S deficiency generally has two causes, a silenced gene or a mutation that results in reduced free protein S antigen levels and activity (18). The prevalence of protein S deficiency in the general population remains unknown. Among patients with a history of VTE in the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis case–control study, 0.9% had protein S deficiency below the level thought to be associated with VTE (31). Detection of protein S deficiency using activity assays alone is subject to substantial variability because of fluctuating levels of protein S binding protein in pregnancy (32). Therefore, screening in nonpregnant women is more reliable, and planned testing should be deferred until remote from a recent birth

or miscarriage to allow for return to normal protein S levels. Among those with a positive family history and documented protein S deficiency, the risk of VTE in pregnancy has been reported to be 5–7% (29, 33). As with protein C deficiency, homozygous protein S deficiency may result in neonatal purpura fulminans (30).

Antithrombin Deficiency

Antithrombin deficiency is highly thrombogenic but rare. The more than 250 associated mutations can decrease gene transcription, leading to reductions in antigen level and activity, or alter structure and function, leading to normal antigen levels but decreased activity (18). The very rare homozygous state is associated with little or no antithrombin activity. The prevalence of heterozygous antithrombin deficiency is approximately 1 per 2,500 members of the general population. Differences in the prevalence of antithrombin deficiency by racial or ethnic group are not known. In nonpregnant patients, the risk of VTE among antithrombin-deficient patients is increased more than 25-fold.

Hemostatic changes of pregnancy, including a decrease in antithrombin levels, may increase the thrombogenic potential of inherited antithrombin deficiency (28, 33). However, the absolute risk is lower in the absence of a positive personal or family history of thromboembolism (20). Similarly, the degree of risk is dependent on the antithrombin level. More severe deficiencies are associated with higher risk of VTE (20). Among women with no prior VTE and a mild antithrombin deficiency (activity between 70% and 85%), the risk of thromboembolism in pregnancy ranges from 0.2% to 0.4%. In contrast, among pregnant women with known familial thrombophilia, a history of thromboembolism, and severe antithrombin deficiency (less than 60% activity), the risk may be as high as 40% (20).

A systematic review of the effect of asymptomatic (with a family history but no personal history of thrombosis) antithrombin deficiency on the risk of VTE in women who are pregnant or in the postpartum period, pooled results from four case–control studies resulting in an estimated odds ratio of 6.09 (95% CI, 1.58–23.43) for thrombosis (34). The pooled estimate is based on 265 cases of thrombosis and 591 controls. In the same systematic review, three cohort studies were identified; however, these could not be pooled because of recurrent pregnancies among the same women. In the cohort studies, the overall incidence of VTE was 11.6% (95% CI, 6.3–19.0%) among asymptomatic antithrombin-deficient patients during pregnancy or the postpartum period, which supports the classification of antithrombin deficiency as a high-risk thrombophilia. A separate Bayesian meta-analysis similarly found an absolute risk of VTE of 7.3% antepartum (95% credible interval 1.8%–15.6%) and 11.1% postpartum (95% credible interval 3.7%–21.0%) in women with antithrombin deficiency (29).

Methylenetetrahydrofolate Reductase Mutations

There is insufficient evidence to support assessment of methylenetetrahydrofolate reductase (*MTHFR*) polymorphisms or measurement of fasting homocysteine levels in the evaluation of a thrombophilic etiology for VTE. Homozygosity for the *MTHFR* gene mutation is the most common cause of hyperhomocysteinemia. Homozygosity for the *MTHFR* C677T and A1298C polymorphisms is present in 10–16% and 4–6% of all Europeans, respectively (35). However, *MTHFR* mutations by themselves do not appear to convey an increased risk of VTE in either nonpregnant (36) or pregnant women (37). Although hyperhomocysteinemia was previously reported to be a modest risk factor of VTE (38, 39), data indicate that elevated homocysteine levels are a weak risk factor of VTE (40). This observation may reflect the folate-replete diet of developed nations, including folate supplementation of flour in the United States. Moreover, intervention studies with vitamin B supplementation in nonpregnant patients show no reduction in VTE (41, 42).

Other Thrombophilias

A variety of other thrombophilias have been described, including alternative mutations in the factor V gene, a promoter mutation in the *PAI*-1 gene, protein Z deficiency, and activity-enhancing mutations in various clotting factor genes. Although they appear to exert little independent risk of VTE, they may exacerbate risk among patients with the aforementioned mutations. However, there is insufficient evidence to recommend testing for these thrombophilias even in the setting of diagnosed VTE.

Inherited Thrombophilias and Adverse Pregnancy Outcomes

A definitive causal link cannot be made between inherited thrombophilias and adverse pregnancy outcomes. Most of the available studies are small case–control and cohort studies assembled in heterogeneous populations, are frequently contradictory, and display potential reporting biases (43–45). Larger prospective cohort studies completed by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network and Stillbirth Collaborative Research Network demonstrate no or weak associations between inherited thrombophilias and adverse pregnancy outcomes (46–48).

Fetal Loss

There are inconsistent associations between any inherited thrombophilias and recurrent pregnancy loss or stillbirth. Whereas meta-analyses and a retrospective cohort study

have revealed an association between inherited thrombophilias and first-trimester pregnancy loss (49–54), prospective cohort studies have found no association between inherited thrombophilias and fetal loss. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network tested low-risk women with a singleton pregnancy less than 14 weeks of gestation and found no increase in the incidence of fetal loss among women heterozygous for factor V Leiden (46). Similar findings of no increased risk of fetal loss were noted for maternal carriers of the prothrombin G20210A gene mutation (47). Recent meta-analyses demonstrated no benefit of treatment with a prophylactic dose of low-molecular-weight heparin to improve the rates of live birth in women with an inherited thrombophilia and a history of pregnancy loss when compared with no treatment or aspirin alone (55, 56). A Cochrane review also concluded that there is insufficient evidence to support the use of anticoagulants (aspirin or low-molecular-weight heparin) in women with recurrent pregnancy loss and an inherited thrombophilia, and advocated for randomized controlled trials to address this question (57).

Regarding fetal death later in pregnancy, the Stillbirth Collaborative Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development conducted a secondary analysis of their prospective population-based case–control study, which demonstrated no association between stillbirth and either prothrombin or *MTHFR* mutations (48). There was, however, a weak association between maternal homozygous factor V Leiden mutation and stillbirth, with 2/405 women with antepartum stillbirths who were homozygous for factor V. The authors concluded that there is insufficient evidence to screen for inherited thrombophilia in the setting of stillbirth.

Preeclampsia

There is insufficient evidence to conclude that inherited thrombophilias are associated with an increased occurrence of preeclampsia. Some clinical studies have reported a link between factor V Leiden and preeclampsia, severe preeclampsia, and preeclampsia before 37 weeks of gestation (58, 59). However, multiple other case–control studies have failed to demonstrate an association between factor V Leiden mutation and preeclampsia (46,60–63).

Meta-analyses yield conflicting results dependent upon the type of studies analyzed. Two meta-analyses of case–control studies found an association between factor V Leiden mutation and preeclampsia. One meta-analysis that included 31 studies with 7,522 patients found an association between factor V Leiden mutation and preeclampsia (pooled odds ratio [OR], 1.81; 95% CI, 1.14–2.87) (64). Another meta-analysis similarly found an association with preeclampsia when including 37 studies with 5,048 preeclampsia patients (pooled OR, 1.60; 95% CI, 1.28–2.00) (65). In both of these meta-analyses women who were heterozygous and homozygous for the gene mutations were analyzed together.

In contrast, a 2016 systematic review and meta-analysis of 10 prospective cohort studies with 21,833 patients to evaluate the association between either factor V Leiden or prothrombin gene mutation and preeclampsia found no association between factor V Leiden and preeclampsia (pooled OR, 1.23; 95% CI, 0.89–1.70) (66). Similarly, a recent prospective cohort study of 7,343 unselected women failed to demonstrate an association between heterozygosity for factor V Leiden or prothrombin gene mutation and a composite adverse outcome of preeclampsia, pregnancy loss, placental abruption or small for gestational age (less than 10th percentile) (45).

Multiple studies also have failed to establish a link between prothrombin G20210A mutation and either preeclampsia or severe preeclampsia (46, 47, 62, 64, 67, 68). However, a 2014 meta-analysis did find an association between prothrombin gene mutation and preeclampsia (pooled OR, 1.81; 95% CI, 1.25–2.63), which is in contrast to the findings of another 2014 study in an unselected population in which no association was noted (45, 65). Although several meta-analyses have suggested an association between protein C and protein S deficiency and preeclampsia, the conclusions are based on a small number of studies with small numbers of participants (69).

Fetal Growth Restriction

Multiple case–control, cohort, and systematic review studies have failed to detect a significant association between factor V Leiden and fetal growth restriction less than the 10th percentile or less than the 5th percentile (58, 62, 70). A similar lack of association was noted between prothrombin G20210A mutation and fetal growth restriction (47, 71, 72). A case–control study among 493 newborns with fetal growth restriction and 472 matched controls found no association between fetal growth restriction and factor V Leiden, prothrombin G20210A mutation, or *MTHFR* mutations (73).

Placental Abruption

Overall, there is insufficient evidence to establish a link between thrombophilias and placental abruption. Prospective cohort analyses of factor V Leiden, prothrombin G20210A, and pregnancy outcome found no association with placental abruption (46, 47). However, a meta-analysis of case–control studies reported an association between placental abruption and both homozygosity and heterozygosity for the factor V Leiden mutation and a link between prothrombin G20210A mutation heterozygosity and placental abruption (69). The Hordaland Homocysteine Study found an association between placental abruption and hyperhomocysteinemia greater than 15 micromol/L (74), but minimal association

between homozygosity for the *MTHFR* C677T polymorphism and placental abruption (75).

Anticoagulation for Prevention of Adverse Pregnancy Outcomes

There is insufficient evidence to recommend anticoagulation as an intervention to prevent adverse pregnancy outcomes among women with inherited thrombophilias. Prior studies focus predominantly on anticoagulation as a strategy for prevention of placenta-mediated adverse outcomes. A recent meta-analysis of individual patient-level data from eight randomized trials assessed the effect of low-molecular-weight heparin on prevention of adverse pregnancy outcomes. Of the women included in the meta-analysis, 42% (403/963) had a thrombophilia (76). Eligible women were those who were currently pregnant and had a history of adverse pregnancy outcomes. Overall, low-molecular-weight heparin did not reduce the rate of recurrent placenta-mediated pregnancy complications including small for gestational age (less than 5th percentile), pregnancy loss at or after 20 weeks of gestation, early onset (less than 34 weeks of gestation) preeclampsia or preeclampsia with severe features, or placental abruption leading to delivery when compared with placebo. Two randomized trials included in this meta-analysis enrolled only women with a thrombophilia (77, 78). In the Thrombophilia in Pregnancy Prophylaxis trial there was no reduction in adverse pregnancy outcome with low-molecular-weight heparin compared with placebo (risk difference, 1.8%; 95% CI, 10.6% to 7.1% in intention-to-treat analysis) (77). However, in another randomized controlled trial there was a reduction in risk of adverse pregnancy outcome when administering low-molecular-weight heparin versus placebo among women with a thrombophilia and a history of delivery before 34 weeks of gestation with hypertensive disease, or small-for-gestational-age infants, or both (risk difference, 8.7%; 95% CI, 1.9–15.5%) (78). Given the inconsistency in findings, and lack of effect in the meta-analysis, anticoagulation is not recommended for prevention of adverse pregnancy outcomes. Further research may delineate subgroups of women with a thrombophilia in which anticoagulation may be beneficial.

Clinical Considerations and Recommendations

▶ *Who are candidates for thrombophilia evaluation?*

Screening for inherited thrombophilias is useful only when results will affect management decisions, and it is not useful in situations in which treatment is indicated for other risk factors (79).

Targeted assessment for inherited thrombophilia may be considered in the following clinical scenarios:

- A personal history of VTE, with or without a recurrent risk factor, and no prior thrombophilia testing. In a population-based study, the recurrence risk of VTE in untreated pregnant women differed based on whether the prior embolism was associated with a recurrent (eg, pregnancy, estrogen containing contraceptives) or nonrecurrent (eg, fractures, surgery, prolonged immobilization) risk factor (4.5% versus 2.7%; RR, 1.71; 95% CI, 1.0–2.8) (21). Inherited thrombophilia increases this risk to varying degrees dependent on the type of thrombophilia (Table 1).
- A first-degree relative (eg, parent or sibling) with a history of high-risk inherited thrombophilia. In this setting, targeted testing for the known thrombophilia can be considered if testing will influence management.

In other situations, thrombophilia testing is not routinely recommended. Specifically, screening for inherited thrombophilias is not recommended for women with a history of fetal loss or adverse pregnancy outcomes including abruption, preeclampsia, or fetal growth restriction because there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low-molecular-weight-heparin prevents recurrence in these patients, and a causal association has not been established (57). Although testing for inherited thrombophilias is not recommended, testing for the acquired antibodies present in antiphospholipid syndrome should be considered in the setting of recurrent pregnancy loss or stillbirth (80).

▶ *What laboratory tests are recommended for thrombophilia screening among women with personal histories of venous thromboembolism and no prior thrombophilia testing?*

Among women with personal histories of VTE, recommended screening tests for inherited thrombophilias should include factor V Leiden mutation; prothrombin G20210A mutation; and antithrombin, protein S, and protein C deficiencies (Table 2). Thrombophilia screening also includes testing for acquired thrombophilia with antiphospholipid antibodies (80). Whenever possible, laboratory testing should be performed remote (after 6 weeks) from the thrombotic event and while the patient is not pregnant and not taking anticoagulation or hormonal therapy.

Ideally, protein S deficiency should be assessed initially by performing a functional assay remote from

pregnancy. A value less than 55% should be followed up by assessing free protein S levels. In the nonpregnant state, a free protein S antigen value less than 55% is consistent with protein S deficiency. In pregnancy, it is unclear what protein S activity value is diagnostic, but free protein S cutoffs of less than 30% and less than 24% may be used in the second and third trimesters, respectively (4).

Because of the lack of association between either heterozygosity or homozygosity for the *MTHFR* C677T polymorphism and any negative pregnancy outcomes, including any increased risk of VTE (43, 81), screening with either *MTHFR* mutation analyses or fasting homocysteine levels is not recommended.

▶ *In which patients should anticoagulants be considered to prevent venous thromboembolism?*

All patients with inherited thrombophilias should undergo individualized risk assessment, which may modify management decisions regarding VTE prevention. Risk assessment algorithms exist to evaluate whether women who are pregnant or in the postpartum period with inherited thrombophilias could benefit from anticoagulants to prevent VTE (82, 83). The decision to use anticoagulants in women with inherited thrombophilias is influenced by personal history of VTE, severity of inherited thrombophilia (Table 3), family history of VTE, and additional risk factors such as cesarean delivery, obesity, and prolonged immobility (21, 82, 83).

There is poor consensus among existing guidelines as to what should be classified as a "high-risk" or "low-risk" thrombophilia (21, 82, 83). Overall recommendations are limited by the quality of existing evidence with a high reliance on case–control studies. In an effort to provide clinical guidance in the setting of contradictory national guidelines, a group of experts formed an Anticoagulation Forum and produced a consensus statement regarding the need for prophylaxis in women with an inherited thrombophilia during pregnancy and the postpartum period (84). These authors recommended prophylaxis if the risk of VTE was 3% or greater. Notably, this threshold was determined by consensus opinion, and significantly affected the recommendations. The degree of acceptable risk likely differs for individual patients and requires a discussion of the risks and benefits of anticoagulation in each unique clinical scenario.

A 2017 meta-analysis of 36 studies found that the absolute risk of VTE exceeded 3% only for women with antithrombin, protein C, and protein S deficiencies, or homozygosity for factor V Leiden (29). The absolute risk of thromboembolism in women who are homozygous for the prothrombin gene mutation could not be assessed with the available studies. Notably all women with antithrombin, protein C, and protein S deficiency included in this meta-analysis also had a family history of VTE, which is an additional risk factor for VTE. Existing guidelines vary regarding the classification of antithrombin, protein C, and protein S deficiency as low-risk or high-risk thrombophilias. Family history of thromboembolism increases the risk of thromboembolism in pregnancy and may have contributed to the observed increased absolute risk of thromboembolism in this meta-analysis.

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)	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.

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 duration of therapy, lactation, and patient preference.

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

*Postpartum treatment levels should be equal to antepartum treatment.

†Low-risk thrombophilia: factor V Leiden heterozygous; prothrombin G20210A heterozygous; protein C or protein S deficiency.

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

§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.

Even in the absence of other risk factors, women who are known to be homozygous for the factor V Leiden mutation or prothrombin gene mutation should receive pharmacologic prophylaxis during pregnancy and the postpartum period given the high risk of VTE (21). Similarly, based on National Partnership for Maternal Safety recommendations, women with antithrombin deficiency and women who are heterozygous for factor V and the prothrombin gene mutation are considered high risk of VTE and should receive pharmacologic prophylaxis in the absence of other risk factors (83). Decision-making regarding the need for pharmacologic prophylaxis for other lower risk thrombophilias (factor V Leiden heterozygous, prothrombin G20210A heterozygous, protein C or S deficiency) is based on the presence or absence of other risk factors and can be made in a multidisciplinary fashion with involvement of maternal–fetal medicine subspecialists or hematologists. Treatment recommendations are listed in Table 3.

Women deemed to require pharmacologic prophylaxis during pregnancy will typically continue anticoagulation for at least 6 weeks postpartum (82). Women with recurrent VTE events or other indications for life-long full anticoagulation should receive adjusted-dose low-molecular-weight heparin throughout pregnancy with transition back to maintenance anticoagulation postpartum (21).

▶ *What anticoagulant regimens are available for pregnant women?*

Neither low-molecular-weight heparin nor unfractionated heparin cross the placenta, and both can be used in pregnancy. Vitamin K antagonists should be avoided in pregnancy with the possible exception of prevention of thromboembolism in women with a mechanical heart valve (85–87). Low-molecular-weight heparin is preferred over unfractionated heparin given its longer half-life, more predictable dose response, and improved maternal safety profile (21, 88, 89). Dosage is based on the severity of thrombophilia (Table 3) and may be influenced by the presence of other risk factors for VTE (obesity, cesarean delivery, family history, history of VTE). Prophylactic, intermediate, and adjusted-dose (therapeutic) anticoagulant regimens are in Table 4. In addition, antithrombin concentrates can be used in antithrombin-deficient patients who are refractory to standard anticoagulant therapy or as part of a multidisciplinary plan for prophylaxis or treatment of VTE (90, 91).

The increased risk of VTE in pregnancy is present from the first trimester (92, 93). Therefore, initiation of anticoagulant regimens should occur upon confirmation of a viable pregnancy, or as early in pregnancy as possible (82).

Maternal weight will be used to calculate a dose of low-molecular-weight heparin in adjusted-dose regimens. However, there is insufficient evidence to recommend changing the dose based on weight when using prophylactic regimens. Similarly, routine assessment of anti-Xa levels in the setting of prophylactic anticoagulation is not recommended (21), and decisions regarding prophylactic dosage can be made on a case-by-case basis.

For women requiring adjusted-dose anticoagulation, an initial dose can be calculated based on maternal weight (Table 4) with a goal anti-Xa level of 0.6–1.0 units/mL 4 hours after injection (21). The need to perform routine anti-Xa levels is controversial even in the setting of adjusted-dose therapy. Because dose adjustment during pregnancy has not been shown to increase the safety or efficacy of low-molecular-weight heparin, serial assessment of anti-Xa levels is largely unnecessary (21) but can be considered on a case-by-case basis. If using unfractionated heparin to achieve therapeutic anticoagulation, mid-interval activated partial thromboplastin time (aPTT) levels should be checked in order to ensure therapeutic dosage (21). Consultation with a maternal–fetal medicine subspecialist or hematologist may be helpful in tailoring the anticoagulation plan.

Almost all women who require antepartum anticoagulation will be continued on therapy postpartum (Table 3). Some women who require anticoagulation beyond 6 weeks postpartum will be transitioned to warfarin after delivery. Unfractionated heparin, low-molecular-weight heparin, and warfarin are compatible with breastfeeding (94–96).

Oral direct thrombin inhibitors (dabigatran) and anti-Xa inhibitors (rivaroxaban, apixaban) should be avoided in pregnancy and lactation because there are insufficient data to evaluate safety for the woman, fetus, and breastfeeding neonate (84).

▶ *What is appropriate peripartum management for thrombophilic patients?*

The presence of a thrombophilia alone is not an indication for induction outside of standard obstetric indications. However, induction of labor at term can be used for timing of discontinuation of anticoagulation to facilitate neuraxial anesthesia if desired. The plan for delivery should take into account a discussion with the patient about avoiding an unwanted coagulation effect during delivery and options for analgesia or anesthesia before delivery. The Society for Obstetric Anesthesia and Perinatology (SOAP) has published consensus guidelines addressing thromboprophylaxis and neuraxial anesthetic considerations specifically in the obstetric population (97). In addition to making specific management recommendations, they recommend that every unit have a protocol for when pregnant women and women in the postpartum period should have anticoagulant medications held and when women receiving thromboprophylaxis are eligible for neuraxial anesthesia.

In general, adjusted-dose low-molecular-weight heparin should be held for 24 hours, and prophylactic low-molecular-weight heparin for 12 hours before induction of labor to facilitate neuraxial anesthesia placement (97). Alternatively, consideration can be given to substituting a comparable dose of unfractionated heparin as delivery approaches because its shorter half-life may improve the likelihood that the patient will be a candidate for neuraxial anesthesia during labor and delivery. However, similar to the interval from last dose for prophylactic low-molecular-weight heparin, SOAP guidelines recommend a 12-hour interval from last dose of unfractionated heparin if the dose is more than 7,500 units, in addition to laboratory testing to verify normal aPTT (97). Ultimately, the goal is to optimize appropriate anticoagulation for the patient while still allowing neuraxial anesthesia when desired. The use of sequential compression devices should be considered for patients with a known thrombophilia intrapartum and until they are fully ambulatory postpartum (83). All women undergoing cesarean delivery should have sequential

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
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.

compression devices at a minimum, with consideration for pharmacologic prophylaxis depending on the type of thrombophilia and other risk factors (Table 3).

Patients receiving anticoagulants should be instructed to withhold their injections at the onset of labor. Patients receiving unfractionated heparin or low-molecular-weight heparin who require rapid reversal of the anticoagulant effect for delivery can be treated with protamine sulfate (98). Dosing of protamine sulfate is dependent on the route of administration and whether the patient is receiving unfractionated heparin or low-molecular-weight heparin and the route these medications are being administered (98). Only partial neutralization of low-molecular-weight heparin can be achieved with protamine sulfate.

▶ *What is the appropriate management of thrombophilic patients who require postpartum anticoagulation therapy?*

Postpartum doses of unfractionated heparin or low-molecular-weight heparin should be equal to antepartum therapy. The optimal time to restart anticoagulation therapy postpartum is unclear. A reasonable approach to minimize bleeding complications is to restart unfractionated heparin or low-molecular-weight heparin no

sooner than 4–6 hours after vaginal delivery or 6–12 hours after cesarean delivery. Timing of reinitiation of anticoagulation should be made in conjunction with anesthesiology for women who used neuraxial anesthesia during delivery (99).

To avoid paradoxical thrombosis and skin necrosis from the early anti-protein C effect of warfarin, women who will be treated with warfarin should be bridged with adjusted-dose low-molecular-weight heparin or unfractionated heparin until an international normalized ratio in the therapeutic range (2.0–3.0) is achieved for 2 consecutive days. Warfarin can be started concurrently with adjusted-dose heparin compounds in the postpartum period. Initial dose of warfarin is 5 mg daily for 2 days, with subsequent doses determined by monitoring the international normalized ratio. Warfarin, low-molecular-weight heparin, and unfractionated heparin do not accumulate in breast milk and do not induce an anticoagulant effect in the infant; therefore, these anticoagulants may be used in women who breastfeed (94–96).

▶ *What postpartum contraceptive options are appropriate for women with thrombophilias?*

The risk of VTE among women with an inherited thrombophilia is increased with the use of estrogen-containing oral contraceptives. The relative risk of an initial thromboembolic event is increased above baseline for factor V Leiden heterozygotes (RR, 2.47–15.04), prothrombin gene mutation heterozygotes (RR, 3.60–8.63), factor V Leiden and prothrombin gene heterozygotes (RR, 3.79–76.47), protein C deficiency (RR, 1.7–23.9), protein S deficiency (RR, 1.4–17.1), and antithrombin deficiency (RR, 1.4–115.8) (79). However, the absolute annualized risk of thromboembolism with a thrombophilia and estrogen-containing contraceptive use remains low with estimates ranging from 0.1% to 7.1% (79). The relative risks of thromboembolism with high-risk thrombophilias such as homozygosity for factor V Leiden or homozygosity for prothrombin gene mutation are unknown (79).

Alternative methods of contraception such as intrauterine devices (including those containing progestin), progestin-only pills or implants, and barrier methods should be considered for women with known inherited thrombophilias. However, screening all women for thrombophilias before initiating combination contraception is not recommended given a low absolute risk of thromboembolism even with a thrombophilia, and the large number of women (nearly half a million assuming baseline incidence of fatal embolism of 6 per 100,000) who would need to be screened in order to prevent one death from embolism (100, 101).

Summary of Recommendations

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Screening for inherited thrombophilias is not recommended for women with a history of fetal loss or adverse pregnancy outcomes including abruption, preeclampsia, or fetal growth restriction because there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low-molecular-weight heparin prevents recurrence in these patients.
- Because of the lack of association between either heterozygosity or homozygosity for the *MTHFR* C677T polymorphism and any negative pregnancy outcomes, including any increased risk of VTE, screening with either *MTHFR* mutation analyses or fasting homocysteine levels is not recommended.
- Warfarin, low-molecular-weight heparin, and unfractionated heparin do not accumulate in breast milk and do not induce an anticoagulant effect in the infant; therefore, these anticoagulants may be used in women who breastfeed.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Among women with personal histories of VTE, recommended screening tests for inherited thrombophilias should include factor V Leiden mutation; prothrombin G20210A mutation; and antithrombin, protein S, and protein C deficiencies.
- All patients with inherited thrombophilias should undergo individualized risk assessment, which may modify management decisions regarding VTE prevention.

For More Information

The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at www.acog.org/More-Info/ThrombophiliasInPregnancy.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists' endorsement of the organization, the organization's website, or the content of the resource. The resources may change without notice.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 to March 2018. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

Published online on June 25, 2018.

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

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