



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

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.

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, Pillny 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.
3. Zotz RB, Gerhardt A, Scharf RE. Inherited thrombophilia and gestational venous thromboembolism. *Best Pract Res Clin Haematol* 2003;16:243–59.
4. Haverkate F, Samama M. Familial dysfibrinogenemia and thrombophilia. Report on a study of the SSC Subcommittee on Fibrinogen. *Thromb Haemost* 1995;73:151–61.
5. Friederich PW, Sanson BJ, Simioni P, Zanardi S, Huisman MV, Kindt I, et al. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis [published erratum appears in *Ann Intern Med* 1997;127:1138]. *Ann Intern Med* 1996;125:955–60.
6. Vossen CY, Preston FE, Conard J, Fontcuberta J, Makris M, van der Meer FJ, et al. Hereditary thrombophilia and fetal loss: a prospective follow-up study. *J Thromb Haemost* 2004;2:592–6.
7. Paidas MJ, Ku DH, Lee MJ, Manish S, Thurston A, Lockwood CJ, et al. Protein Z, protein S levels are lower in patients with thrombophilia and subsequent pregnancy complications. *J Thromb Haemost* 2005;3:497–501.
8. Dykes AC, Walker ID, McMahon AD, Islam SI, Tait RC. A study of Protein S antigen levels in 3788 healthy volunteers: influence of age, sex and hormone use, and estimate for prevalence of deficiency state. *Br J Haematol* 2001;113:636–41.
9. Goodwin AJ, Rosendaal FR, Kottke-Marchant K, Bovill EG. A review of the technical, diagnostic, and epidemiologic considerations for protein S assays. *Arch Pathol Lab Med* 2002;126:1349–66.
10. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e691S–736S.
11. Gerhardt A, Scharf RE, Greer IA, Zotz RB. Hereditary risk factors for thrombophilia and probability of venous thromboembolism during pregnancy and the puerperium. *Blood* 2016;128:2343–9.
12. Rheume M, Weber F, Durand M, Mahone M. Pregnancy-related venous thromboembolism risk in asymptomatic women with antithrombin deficiency: a systematic review. *Obstet Gynecol* 2016;127:649–56.



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 prothrom-

bin 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 non-pregnant 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 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.



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 neutral-

ization 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 abruptio, 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.



References

1. Lockwood CJ, Krikun G, Rahman M, Caze R, Buchwald-er L, Schatz F. The role of decidualization in regulating endometrial hemostasis during the menstrual cycle, gestation, and in pathological states. *Semin Thromb Hemost* 2007;33:111–7. (Level III)
2. Lockwood CJ, Krikun G, Schatz F. The decidua regulates hemostasis in human endometrium. *Semin Reprod Endocrinol* 1999;17:45–51. (Level III)
3. Bremme KA. Haemostatic changes in pregnancy. *Best Pract Res Clin Haematol* 2003;16:153–68. (Level III)
4. Paidas MJ, Ku DH, Lee MJ, Manish S, Thurston A, Lockwood CJ, et al. Protein Z, protein S levels are lower in patients with thrombophilia and subsequent pregnancy complications. *J Thromb Haemost* 2005;3:497–501. (Level II-3)
5. Hellgren M. Hemostasis during normal pregnancy and puerperium. *Semin Thromb Hemost* 2003;29:125–30. (Level III)
6. Andersen BS, Steffensen FH, Sorensen HT, Nielsen GL, Olsen J. The cumulative incidence of Venous Thromboembolism during pregnancy and puerperium—an 11 year Danish population-based study of 63,300 pregnancies. *Acta Obstet Gynecol Scand* 1998;77:170–3. (Level II-3)
7. Gherman RB, Goodwin TM, Leung B, Byrne JD, Hethummi R, Montoro M. Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy. *Obstet Gynecol* 1999;94:730–4. (Level II-3)
8. Lindqvist P, Dahlback B, Marsal K. Thrombotic risk during pregnancy: a population study. *Obstet Gynecol* 1999; 94:595–9. (Level II-3)
9. Simpson EL, Lawrenson RA, Nightingale AL, Farmer RD. Venous thromboembolism in pregnancy and the puerperium: incidence and additional risk factors from a London perinatal database. *BJOG* 2001;108:56–60. (Level II-3)
10. Jacobsen AF, Skjeldestad FE, Sandset PM. Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium—a register-based case-control study. *Am J Obstet Gynecol* 2008;198:233.e1–7. (Level II-3)
11. Liu S, Rouleau J, Joseph KS, Sauve R, Liston RM, Young D, et al. Epidemiology of pregnancy-associated venous thromboembolism: a population-based study in Canada. *J Obstet Gynaecol Can* 2009;31:611–20. (Level II-3)
12. Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011–2013. *Obstet Gynecol* 2017;130:366–73. (Level II-3)
13. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ III. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med* 2005;143: 697–706. (Level II-2)
14. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJM. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. *J Thromb Haemost* 2008;6:632–7. (Level II-2)
15. Pabinger I, Grafenhofer H, Kyrle PA, Quehenberger P, Mannhalter C, Lechner K, et al. Temporary increase in the risk for recurrence during pregnancy in women with a history of venous thromboembolism. *Blood* 2002;100: 1060–2. (Level II-3)
16. Scifres CM, Macones GA. The utility of thrombophilia testing in pregnant women with thrombosis: fact or fiction? *Am J Obstet Gynecol* 2008;199:344.e1–7. (Level III)
17. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4,047 men and women. Implications for venous thromboembolism screening. *JAMA* 1997;277:1305–7. (Level II-3)
18. Franco RF, Reitsma PH. Genetic risk factors of venous thrombosis. *Hum Genet* 2001;109:369–84. (Level III)
19. Gerhardt A, Scharf RE, Beckmann MW, Struve S, Bender HG, Pillny 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. (Level II-3)
20. Zotz RB, Gerhardt A, Scharf RE. Inherited thrombophilia and gestational venous thromboembolism. *Best Pract Res Clin Haematol* 2003;16:243–59. (Level III)
21. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e691S–736S. (Level III)
22. Pabinger I, Grafenhofer H, Kaider A, Kyrle PA, Quehenberger P, Mannhalter C, et al. Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis. *J Thromb Haemost* 2005;3:949–54. (Level II-2)
23. Dziadosz M, Baxi LV. Global prevalence of prothrombin gene mutation G20210A and implications in women's health: a systematic review. *Blood Coagul Fibrinolysis* 2016;27:481–9. (Systematic Review)
24. Pabinger I, Allaart CF, Hermans J, Briet E, Bertina RM. Hereditary protein C-deficiency: laboratory values in transmitters and guidelines for the diagnostic procedure. Report on a study of the SSC Subcommittee on Protein C and Protein S. Protein C Transmitter Study Group. *Thromb Haemost* 1992;68:470–4. (Level II-2)
25. Miletich J, Sherman L, Broze G Jr. Absence of thrombosis in subjects with heterozygous protein C deficiency. *N Engl J Med* 1987;317:991–6. (Level II-3)
26. Bovill EG, Bauer KA, Dickerman JD, Callas P, West B. The clinical spectrum of heterozygous protein C deficiency in a large New England kindred. *Blood* 1989;73: 712–7. (Level II-3)
27. Conard J, Horellou MH, Van Dreden P, Lecompte T, Samama M. Thrombosis and pregnancy in congenital deficiencies in AT III, protein C or protein S: study of 78 women. *Thromb Haemost* 1990;63:319–20. (Level III)
28. De Stefano V, Leone G, Mastrangelo S, Tripodi A, Rodeghiero F, Castaman G, et al. Thrombosis during pregnancy and surgery in patients with congenital deficiency



- of antithrombin III, protein C, protein S. *Thromb Haemost* 1994;71:799–800. (Level III)
29. Croles FN, Nasserinejad K, Duvekot JJ, Kruip MJ, Meijer K, Leebeek FW. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and bayesian meta-analysis. *BMJ* 2017;359:j4452. (Systematic Review and Meta-analysis)
 30. Marlar RA, Neumann A. Neonatal purpura fulminans due to homozygous protein C or protein S deficiencies. *Semin Thromb Hemost* 1990;16:299–309. (Level III)
 31. Pintao MC, Ribeiro DD, Bezemer ID, Garcia AA, de Visser MC, Doggen CJ, et al. Protein S levels and the risk of venous thrombosis: results from the MEGA case-control study. *Blood* 2013;122:3210–9. (Level II-2)
 32. Goodwin AJ, Rosendaal FR, Kottke-Marchant K, Bovill EG. A review of the technical, diagnostic, and epidemiologic considerations for protein S assays. *Arch Pathol Lab Med* 2002;126:1349–66. (Level III)
 33. Friederich PW, Sanson BJ, Simioni P, Zanardi S, Huisman MV, Kindt I, et al. Frequency of pregnancy-related venous thromboembolism in anticoagulant factor-deficient women: implications for prophylaxis [published erratum appears in *Ann Intern Med* 1997;127:1138]. *Ann Intern Med* 1996;125:955–60. (Level II-2)
 34. Rheaume M, Weber F, Durand M, Mahone M. Pregnancy-related venous thromboembolism risk in asymptomatic women with antithrombin deficiency: a systematic review. *Obstet Gynecol* 2016;127:649–56. (Systematic Review)
 35. Peng F, Labelle LA, Rainey BJ, Tsongalis GJ. Single nucleotide polymorphisms in the methylenetetrahydrofolate reductase gene are common in US Caucasian and Hispanic American populations. *Int J Mol Med* 2001;8: 509–11. (Level III)
 36. Domagala TB, Adamek L, Nizankowska E, Sanak M, Szczeklik A. Mutations C677T and A1298C of the 5,10-methylenetetrahydrofolate reductase gene and fasting plasma homocysteine levels are not associated with the increased risk of venous thromboembolic disease. *Blood Coagul Fibrinolysis* 2002;13:423–31. (Level II-3)
 37. McColl MD, Ellison J, Reid F, Tait RC, Walker ID, Greer IA. Prothrombin 20210 G→A, MTHFR C677T mutations in women with venous thromboembolism associated with pregnancy. *BJOG* 2000;107:565–9. (Level III)
 38. den Heijer M, Rosendaal FR, Blom HJ, Gerrits WB, Bos GM. Hyperhomocysteinemia and venous thrombosis: a meta-analysis. *Thromb Haemost* 1998;80:874–7. (Meta-analysis)
 39. Eichinger S. Homocysteine, vitamin B6, the risk of recurrent venous thromboembolism. *Pathophysiol Haemost Thromb* 2003;33:342–4. (Level III)
 40. den Heijer M, Lewington S, Clarke R. Homocysteine, MTHFR and risk of venous thrombosis: a meta-analysis of published epidemiological studies. *J Thromb Haemost* 2005;3:292–9. (Meta-analysis)
 41. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators* [published erratum appears in *N Engl J Med*. 2006;355:746]. *N Engl J Med* 2006;354:1567–77. (Level I)
 42. den Heijer M, Willems HP, Blom HJ, Gerrits WB, Cattaneo M, Eichinger S, et al. Homocysteine lowering by B vitamins and the secondary prevention of deep vein thrombosis and pulmonary embolism: a randomized, placebo-controlled, double-blind trial. *Blood* 2007;109: 139–44. (Level I)
 43. Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe GD, et al. Thrombophilia in pregnancy: a systematic review. *Thrombosis: Risk and economic Assessment of Thrombophilia Screening (TREATS) study*. *Br J Haematol* 2006;132:171–96. (Meta-analysis)
 44. Kosmas IP, Tatsioni A, Ioannidis JP. Association of Leiden mutation in factor V gene with hypertension in pregnancy and pre-eclampsia: a meta-analysis. *J Hypertens* 2003;21:1221–8. (Meta-analysis)
 45. Rodger MA, Walker MC, Smith GN, Wells PS, Ramsay T, Langlois NJ, et al. Is thrombophilia associated with placenta-mediated pregnancy complications? A prospective cohort study. *J Thromb Haemost* 2014;12:469–78. (Level II-2)
 46. Dizon-Townson D, Miller C, Sibai B, Spong CY, Thom E, Wendel G Jr, et al. The relationship of the factor V Leiden mutation and pregnancy outcomes for mother and fetus. *National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*. *Obstet Gynecol* 2005;106:517–24. (Level II-2)
 47. Silver RM, Zhao Y, Spong CY, Sibai B, Wendel G Jr, Wenstrom K, et al. Prothrombin gene G20210A mutation and obstetric complications. *Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units (NICHD MFMU) Network*. *Obstet Gynecol* 2010;115:14–20. (Level II-2)
 48. Silver RM, Saade GR, Thorsten V, Parker CB, Reddy UM, Drews-Botsch C, et al. Factor V Leiden, prothrombin G20210A, and methylene tetrahydrofolate reductase mutations and stillbirth: the Stillbirth Collaborative Research Network. *Am J Obstet Gynecol* 2016;215:468. e1–17. (Level II-2)
 49. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. *Lancet* 2003;361: 901–8. (Meta-analysis)
 50. Dudding TE, Attia J. The association between adverse pregnancy outcomes and maternal factor V Leiden genotype: a meta-analysis. *Thromb Haemost* 2004;91:700–11. (Meta-analysis)
 51. Nelen WL, Blom HJ, Steegers EA, den Heijer M, Eskes TK. Hyperhomocysteinemia and recurrent early pregnancy loss: a meta-analysis. *Fertil Steril* 2000;74:1196–9. (Meta-analysis)
 52. Lissalde-Lavigne G, Fabbro-Peray P, Cochery-Nouvellon E, Mercier E, Ripart-Neveu S, Balducci JP, et al. Factor V Leiden and prothrombin G20210A polymorphisms as risk factors for miscarriage during a first intended pregnancy: the matched case–control “NOHA first” study. *J Thromb Haemost* 2005;3:2178–84. (Level II-2)
 53. Preston FE, Rosendaal FR, Walker ID, Briet E, Berntorp E, Conard J, et al. Increased fetal loss in women with heritable thrombophilia. *Lancet* 1996;348:913–6. (Level II-2)



54. Sergi C, Al Jishi T, Walker M. Factor V Leiden mutation in women with early recurrent pregnancy loss: a meta-analysis and systematic review of the causal association. *Arch Gynecol Obstet* 2015;291:671–9. (Meta-analysis and Systematic Review)
55. Areia AL, Fonseca E, Areia M, Moura P. Low-molecular-weight heparin plus aspirin versus aspirin alone in pregnant women with hereditary thrombophilia to improve live birth rate: meta-analysis of randomized controlled trials. *Arch Gynecol Obstet* 2016;293:81–6. (Meta-analysis)
56. Skeith L, Carrier M, Kaaja R, Martinelli I, Petroff D, Schleussner E, et al. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. *Blood* 2016;127:1650–5. (Meta-analysis)
57. de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. *Cochrane Database of Systematic Reviews* 2014, Issue 7. Art. No.: CD004734. (Systematic Review)
58. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy [published erratum appears in *N Engl J Med* 1999;341:384]. *N Engl J Med* 1999;340:9–13. (Level II-2)
59. Nurk E, Tell GS, Refsum H, Ueland PM, Vollset SE. Factor V Leiden, pregnancy complications and adverse outcomes: the Hordaland homocysteine study. *QJM* 2006;99:289–98. (Level II-2)
60. Currie L, Peek M, McNiven M, Prosser I, Mansour J, Ridgway J. Is there an increased maternal-infant prevalence of Factor V Leiden in association with severe preeclampsia? *BJOG* 2002;109:191–6. (Level II-2)
61. van Pampus MG, Wolf H, Koopman MM, van den Ende A, Buller HR, Reitsma PH. Prothrombin 20210 G: a mutation and Factor V Leiden mutation in women with a history of severe preeclampsia and (H)ELLP syndrome. *Hypertens Pregnancy* 2001;20:291–8. (Level III)
62. D’Elia AV, Driul L, Giacomello R, Colaone R, Fabbro D, Di Leonardo C, et al. Frequency of factor V, prothrombin and methylenetetrahydrofolate reductase gene variants in preeclampsia. *Gynecol Obstet Invest* 2002;53:84–7. (Level II-3)
63. Kahn SR, Platt R, McNamara H, Rozen R, Chen MF, Genest J Jr, et al. Inherited thrombophilia and preeclampsia within a multicenter cohort: the Montreal Preeclampsia Study. *Am J Obstet Gynecol* 2009;200:151.e1–9; discussion e1–5. (Level II-2)
64. Lin J, August P. Genetic thrombophilias and preeclampsia: a meta-analysis. *Obstet Gynecol* 2005;105:182–92. (Meta-analysis)
65. Wang X, Bai T, Liu S, Pan H, Wang B. Association between thrombophilia gene polymorphisms and preeclampsia: a meta-analysis. *PLoS One* 2014;9:e100789. (Meta-analysis)
66. Rodger MA, Betancourt MT, Clark P, Lindqvist PG, Dizon-Townson D, Said J, et al. The association of factor V Leiden and prothrombin gene mutation and placenta-mediated pregnancy complications: a systematic review and meta-analysis of prospective cohort studies. *PLoS Med* 2010;7:e1000292. (Systematic Review and Meta-analysis)
67. Morrison ER, Miedzybrodzka ZH, Campbell DM, Haites NE, Wilson BJ, Watson MS, et al. Prothrombotic genotypes are not associated with pre-eclampsia and gestational hypertension: results from a large population-based study and systematic review. *Thromb Haemost* 2002;87:779–85. (Level II-2)
68. Livingston JC, Barton JR, Park V, Haddad B, Phillips O, Sibai BM. Maternal and fetal inherited thrombophilias are not related to the development of severe preeclampsia. *Am J Obstet Gynecol* 2001;185:153–7. (Level II-3)
69. Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. *Eur J Obstet Gynecol Reprod Biol* 2002;101:6–14. (Meta-analysis)
70. Howley HE, Walker M, Rodger MA. A systematic review of the association between factor V Leiden or prothrombin gene variant and intrauterine growth restriction. *Am J Obstet Gynecol* 2005;192:694–708. (Meta-analysis)
71. Franchi F, Cetin I, Todros T, Antonazzo P, Nobile de Santis MS, Cardaropoli S, et al. Intrauterine growth restriction and genetic predisposition to thrombophilia. *Haematologica* 2004;89:444–9. (Level II-2)
72. Verspyck E, Borg JY, Le Cam-Duchez V, Goffinet F, Degre S, Fournet P, et al. Thrombophilia and fetal growth restriction. *Eur J Obstet Gynecol Reprod Biol* 2004;113:36–40. (Level II-2)
73. Infante-Rivard C, Rivard GE, Yotov WV, Genin E, Guiguet M, Weinberg C, et al. Absence of association of thrombophilia polymorphisms with intrauterine growth restriction. *N Engl J Med* 2002;347:19–25. (Level II-2)
74. Vollset SE, Refsum H, Irgens LM, Emblem BM, Tverdal A, Gjessing HK, et al. Plasma total homocysteine, pregnancy complications, and adverse pregnancy outcomes: the Hordaland Homocysteine study. *Am J Clin Nutr* 2000;71:962–8. (Level II-3)
75. Nurk E, Tell GS, Refsum H, Ueland PM, Vollset SE. Associations between maternal methylenetetrahydrofolate reductase polymorphisms and adverse outcomes of pregnancy: the Hordaland Homocysteine Study. *Am J Med* 2004;117:26–31. (Level II-3)
76. Rodger MA, Gris JC, de Vries JIP, Martinelli I, Rey E, Schleussner E, et al. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. *Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group. Lancet* 2016;388:2629–41. (Meta-analysis)
77. Rodger MA, Hague WM, Kingdom J, Kahn SR, Karovitch A, Sermer M, et al. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. *TIPPS Investigators. Lancet* 2014;384:1673–83. (Level I)
78. de Vries JI, van Pampus MG, Hague WM, Bezemer PD, Joosten JH. Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset preeclampsia in women with inheritable thrombophilia: the



- FRUIT-RCT. FRUIT Investigators [published erratum appears in *J Thromb Haemost* 2015;13:327]. *J Thromb Haemost* 2012;10:64–72. (Level I)
79. Stevens SM, Woller SC, Bauer KA, Kasthuri R, Cushman M, Streiff M, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. *J Thromb Thrombolysis* 2016;41:154–64. (Level III)
 80. Antiphospholipid syndrome. Practice Bulletin No. 132. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2012;120:1514–21. (Level III)
 81. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol* 2006;194:1311–5. (Level III)
 82. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green Top Guideline No. 37a. Royal College of Obstetricians and Gynaecologists. London (UK): RCOG; 2015. (Level III)
 83. D'Alton ME, Friedman AM, Smiley RM, Montgomery DM, Paidas MJ, D'Oria R, et al. National Partnership for Maternal Safety: consensus bundle on venous thromboembolism. *Obstet Gynecol* 2016;128:688–98. (Level III)
 84. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. *J Thromb Thrombolysis* 2016;41:92–128. (Level III)
 85. Nassar AH, Hobeika EM, Abd Essamad HM, Taher A, Khalil AM, Usta IM. Pregnancy outcome in women with prosthetic heart valves. *Am J Obstet Gynecol* 2004;191:1009–13. (Level III)
 86. Sadler L, McCowan L, White H, Stewart A, Bracken M, North R. Pregnancy outcomes and cardiac complications in women with mechanical, bioprosthetic and homograft valves. *BJOG* 2000;107:245–53. (Level III)
 87. van Hagen IM, Roos-Hesselink JW, Ruys TP, Merz WM, Goland S, Gabriel H, et al. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). ROPAC Investigators and the EURObservational Research Programme (EORP) Team. *Circulation* 2015;132:132–42. (Level II-3)
 88. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood* 2005;106:401–7. (Systematic Review)
 89. Pettila V, Leinonen P, Markkola A, Hiilesmaa V, Kaaja R. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. *Thromb Haemost* 2002;87:182–6. (Level I)
 90. James AH, Konkle BA, Bauer KA. Prevention and treatment of venous thromboembolism in pregnancy in patients with hereditary antithrombin deficiency. *Int J Womens Health* 2013;5:233–41. (Level III)
 91. Refaei M, Xing L, Lim W, Crowther M, Boonyawat K. Management of venous thromboembolism in patients with hereditary antithrombin deficiency and pregnancy: case report and review of the literature. *Case Rep Hematol* 2017;2017:9261351. (Level III)
 92. Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and the leg of presentation. *Obstet Gynecol Surv* 1999;54:265–71. (Meta-analysis)
 93. James AH, Tapson VF, Goldhaber SZ. Thrombosis during pregnancy and the postpartum period. *Am J Obstet Gynecol* 2005;193:216–9. (Level III)
 94. Clark SL, Porter TF, West FG. Coumarin derivatives and breast-feeding. *Obstet Gynecol* 2000;95:938–40. (Level III)
 95. Orme ML, Lewis PJ, de Swiet M, Serlin MJ, Sibeon R, Baty JD, et al. May mothers given warfarin breast-feed their infants? *Br Med J* 1977;1:1564–5. (Level III)
 96. Richter C, Sitzmann J, Lang P, Weitzel H, Huch A, Huch R. Excretion of low molecular weight heparin in human milk. *Br J Clin Pharmacol* 2001;52:708–10. (Level III)
 97. Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, et al. The Society for Obstetric Anesthesia and Perinatology consensus statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. Members of the SOAP VTE Taskforce. *Anesth Analg* 2017. (Level III)
 98. Holst J, Lindblad B, Bergqvist D, Garre K, Nielsen H, Hedner U, et al. Protamine neutralization of intravenous and subcutaneous low-molecular-weight heparin (tinzaparin, Logiparin). An experimental investigation in healthy volunteers. *Blood Coagul Fibrinolysis* 1994;5:795–803. (Level II-3)
 99. Thromboembolism in pregnancy. Practice Bulletin No. 196. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2018;132:e1–17. (Level III)
 100. Price DT, Ridker PM. Factor V Leiden mutation and the risks for thromboembolic disease: a clinical perspective. *Ann Intern Med* 1997;127:895–903. (Level III)
 101. Comp PC, Zacur HA. Contraceptive choices in women with coagulation disorders. *Am J Obstet Gynecol* 1993;168:1990–3. (Level III)



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.

Copyright 2018 by the American College of Obstetricians and Gynecologists. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, posted on the Internet, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher.

Requests for authorization to make photocopies should be directed to Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400.

American College of Obstetricians and Gynecologists
409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920

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



This information is designed as an educational resource to aid clinicians in providing obstetric and gynecologic care, and use of this information is voluntary. This information should not be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. It is not intended to substitute for the independent professional judgment of the treating clinician. Variations in practice may be warranted when, in the reasonable judgment of the treating clinician, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology. The American College of Obstetricians and Gynecologists reviews its publications regularly; however, its publications may not reflect the most recent evidence. Any updates to this document can be found on www.acog.org or by calling the ACOG Resource Center.

While ACOG makes every effort to present accurate and reliable information, this publication is provided “as is” without any warranty of accuracy, reliability, or otherwise, either express or implied. ACOG does not guarantee, warrant, or endorse the products or services of any firm, organization, or person. Neither ACOG nor its officers, directors, members, employees, or agents will be liable for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with this publication or reliance on the information presented.

All ACOG committee members and authors have submitted a conflict of interest disclosure statement related to this published product. Any potential conflicts have been considered and managed in accordance with ACOG’s Conflict of Interest Disclosure Policy. The ACOG policies can be found on acog.org. For products jointly developed with other organizations, conflict of interest disclosures by representatives of the other organizations are addressed by those organizations. The American College of Obstetricians and Gynecologists has neither solicited nor accepted any commercial involvement in the development of the content of this published product.