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Inherited Thrombophilias in Pregnancy

Inherited thrombophilias are associated with an increased risk of venous thromboembolism and also 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.

Background

The Hemostatic Paradox of Pregnancy

Pregnancy poses a particularly complex hemostatic challenge. Successful pregnancy requires the avoidance of hemorrhage during implantation, endovascular cytotrophoblast remodeling of maternal spiral arteries, and during the third stage of labor it also requires the maintenance of a fluid uteroplacental circulation. Maintaining hemostatic balance during pregnancy requires alterations in both 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 the maintenance of gestational hemostasis is seen in the 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).

Pregnancy 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. Thus, it is not surprising that venous thromboembolism complicates approximately 1 in 1,600 births and is a leading cause of maternal morbidity in the United States (6, 7).

There is a strong association between inherited thrombophilias and venous thromboembolism, which makes detection of these mutations a logical target for prevention strategies (Table 1). However, it is controversial whether there is an association between inherited thrombophilias and uteroplacental thrombosis that lead to adverse pregnancy outcomes such as fetal loss, preeclampsia, fetal growth restriction, and placental abruption (8). This possible association has resulted in increased screening for thrombophilias in pregnancy, although there has been no confirmation of treatment benefits.

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Table 1. Risk of Venous Thromboembolism With Different 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	0.5–1.2	10	40	1–4
Factor V Leiden homozygote	<1	4	17	2	1–4
Prothrombin gene heterozygote	2–5	<0.5	>10	17	1–4
Prothrombin gene homozygote	<1	2–4	>17	0.5	1–4
Factor V Leiden/prothrombin double heterozygote	0.01	4–5	>20	1–3	1–4
Antithrombin III activity (<60%)	0.02	3–7	40	1	1, 5, 6
Protein C activity (<50%)	0.2–0.4	0.1–0.8	4–17	14	1, 5, 7
Protein S free antigen (<55%)	0.03–0.13	0.1	0–22	3	1, 8–10

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 dysfibrinogenaemia and thrombophilia. Report on a study of the SSC Subcommittee on fibrinogen. Thromb Haemost 1995;73:151–61.
5. Carraro P. Guidelines for the laboratory investigation of inherited thrombophilias. Recommendations for the first level clinical laboratories. European Communities Confederation of Clinical Chemistry and Laboratory Medicine, Working Group on Guidelines for Investigation of Disease. Clin Chem Lab Med 2003;41:382–91.
6. 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 errata appear in Ann Intern Med 1997;127:1138; Ann Intern Med 1997;126:835]. Ann Intern Med 1996;125:955–60.
7. 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.
8. 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.
9. 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.
10. 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.

Prevalence of Common Inherited Thrombophilias

Factor V Leiden

The prevalence of the factor V Leiden mutation in European populations is approximately 5% (9). Although the mutation is virtually absent in black Africans, Chinese, Japanese, and other Asian populations, it is present in 3% of African Americans whose ancestors are not recent immigrants. 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 venous thromboembolism during pregnancy; however, the risk of venous thromboembolism among pregnant women who are heterozygous for factor V Leiden without a personal history of venous thromboembolism or an affected first-degree relative with a thrombotic episode before age 50 years while increased above the baseline pregnancy risk, is estimated to be no more than 5–12/1,000 deliveries (10–12). In contrast, this risk increases to up to 10% among pregnant women heterozygous for the factor V Leiden mutation with a personal history of venous thromboembolism (11–13). A woman who is heterozygous for factor V Leiden with only an affected first-degree relative but no personal history of venous thromboembolism, however, only has a slightly higher risk of venous thromboembolism during pregnancy (15/1,000 deliveries) than that conferred by her thrombophilia alone (11, 12). Pregnant women who are homozygous for factor V Leiden without a personal history of venous thromboembolism or an affected first-degree relative have a 1–2% risk for venous thromboembolism, whereas those with such a history have a 17% risk (11).

Prothrombin *G20210A*

The prothrombin *G20210A* mutation is a point mutation that results in elevated circulating prothrombin levels (9). 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 venous thromboembolism in pregnancy (10). As with factor V Leiden, a personal history of venous thromboembolism increases the risk of venous thromboembolism 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 venous thromboembolism during pregnancy; for a carrier with a personal history of venous thromboembolism, the risk increases to at least 10% (10, 12). Also, as with factor V Leiden, heterozygous prothrombin gene mutation carriers without a personal history of venous thromboembolism have only a slight increase in risk during pregnancy if an affected first-degree relative exists (12). Pregnant women who are homozygous for the prothrombin *G20210A* mutation without a personal or positive family history have a 2–3% risk of venous thromboembolism in pregnancy, whereas such a history confers a substantially greater risk. The combination of factor V Leiden and prothrombin *G20210A* mutations has synergistic hypercoagulable effects. Those who are heterozygous for this combination, although present in only 1 per 10,000 patients, have a 4–5% risk of venous thromboembolism even without a personal or positive family history (10, 11).

Protein C Deficiency

Protein C deficiency has been linked to more than 160 distinct mutations that produce a highly variable phenotype (9). The prevalence of protein C deficiency is 0.2–0.3% when determined by a functional assay with a cutoff of 50–60%. The risk of venous thromboembolism in pregnancy among the typical protein C deficient patient with a personal or family history has been reported to be 2–7% (14, 15). Although rare, newborns who are homozygous for protein C deficiency will develop neonatal purpura fulminans and require lifetime anticoagulation therapy (16).

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 (9). Detection of protein S deficiency using activity assays alone is subject to substantial variability due to fluctuating levels of protein S binding protein in pregnancy (17). Therefore, screening in nonpregnant women is more reliable (18). However, 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 (4). Among those with a positive family history, the risk of venous thromboembolism in pregnancy has been reported to be 6–7% (19). As with protein C deficiency, homozygous protein S deficiency results in neonatal purpura fulminans (16).

Antithrombin Deficiency

Antithrombin deficiency is highly thrombogenic but rare. The more than 250 associated mutations can decrease gene transcription, leading to reductions in both antigen level and activity, or alter structure and function leading to normal antigen levels but decreased activity (9, 20). The very rare homozygous state is associated with little or no antithrombin activity. The prevalence of antithrombin deficiency is approximately 1 per 2,500 patients (20, 21). In nonpregnant patients, the risk of venous thromboembolism among antithrombin-deficient patients is increased more than 25-fold (20). Pregnancy may increase the thrombogenic potential of antithrombin deficiency substantially (15, 19). However, this risk may be much lower in the absence of a positive personal or family history (11).

Methylenetetrahydrofolate Reductase Mutations

Homozygosity for the methylenetetrahydrofolate reductase (*MTHFR*) gene mutations 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 (22). However, *MTHFR* mutations by themselves do not appear to convey an increased risk for venous thromboembolism in either nonpregnant (23) or pregnant women (24). Although hyperhomocysteinemia was previously reported to be a modest risk factor of venous thromboembolism (25, 26), recent data indicate that elevated homocysteine levels are a weak risk factor of venous thromboembolism (27). 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 venous thromboembolism (28, 29). Thus, there is insufficient evidence to support assessment of MTHFR polymorphisms or measurement of fasting homocysteine levels in the evaluation of a thrombophilic etiology for venous thromboembolism and, therefore, it is not recommended.

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 venous thromboembolism, they may exacerbate risk among patients with the aforementioned mutations. However, there is insufficient evidence to recommend screening for these thrombophilias.

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 (30, 31).

Fetal Loss

Whereas meta-analyses and a retrospective cohort study have revealed an association between inherited thrombophilias and first-trimester pregnancy loss (32–36), 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's Maternal–Fetal Medicine Units Network tested low-risk women with a singleton pregnancy less than 14 weeks of gestation. The Maternal–Fetal Medicine Units Network identified 134 women who were heterozygous for factor V Leiden among 4,885 pregnant women, and found no increase in the incidence of fetal loss (37). Similar findings of no increased risk of fetal loss were noted for maternal carriers of the prothrombin *G20210A* gene mutation (38).

Preeclampsia

Some clinical studies have reported a link between factor V Leiden and preeclampsia, severe preeclampsia, and preeclampsia before 37 weeks of gestation (39, 40). However, multiple other case–control studies have failed to demonstrate an association between factor V Leiden mutation and preeclampsia (37, 41–44).

Multiple studies also have failed to establish a link between prothrombin *G20210A* mutation and either preeclampsia or severe preeclampsia (37, 38, 43, 45–47). Several meta-analyses have suggested an association between protein C and protein S deficiency and preeclampsia; however, these conclusions are based on a small number of studies that also contained small numbers of participants (48). There is insufficient evidence to conclude that inherited thrombophilias are associated with an increased occurrence of preeclampsia.

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 (39, 43, 49). A similar lack of association was noted between prothrombin *G20210A* mutation and fetal growth restriction (38, 50, 51). 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 (52).

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 (37, 38). 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 (48). The Hordaland Homocysteine Study found an association between placental abruption and hyperhomocysteinemia greater than 15 micromol/L (53), but minimal association between homozygosity for the MTHFR C677T polymorphism and placental abruption (54).

Clinical Considerations and Recommendations

▶ *Who are candidates for thrombophilia evaluation?*

Screening for thrombophilias is controversial. It is useful only when results will affect management decisions, and is not useful in situations where treatment is indicated for other risk factors. Screening may be considered in the following clinical settings:

- A personal history of venous thromboembolism that was associated with a nonrecurrent risk factor (eg, fractures, surgery, and prolonged immobilization). The recurrence risk among untreated pregnant women with such a history and a thrombophilia was 16% (odds ratio, 6.5; 95% confidence interval, 0.8–56.3) (55).
- A first-degree relative (eg, parent or sibling) with a history of high-risk thrombophilia.

In other situations, thrombophilia testing is not routinely recommended. Testing for inherited thrombophilias in women who have experienced recurrent fetal

loss or placental abruption is not recommended because it is unclear if anticoagulation therapy reduces recurrence. Although there may be an association in these cases, there is insufficient clinical evidence that antepartum prophylaxis with unfractionated heparin or low molecular weight heparin (LMWH) prevents recurrence in these patients (56). However, screening for antiphospholipid antibodies may be appropriate in patients experiencing fetal loss (see Practice Bulletin No. 132, Antiphospholipid Syndrome, December 2012). In addition, there is insufficient evidence of an association and, therefore, insufficient evidence to either screen for or treat women with inherited thrombophilias and obstetric histories that include complications such as fetal growth restriction or preeclampsia.

▶ *What laboratory tests are recommended for thrombophilia screening?*

Recommended screening tests for inherited thrombophilias should include factor V Leiden mutation; prothrombin *G20210A* mutation; and antithrombin, protein S, and protein C deficiencies as listed in Table 2. 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.

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 for venous thromboembolism (57, 30), screening with either *MTHFR* mutation analyses or fasting homocysteine levels is not recommended.

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

Given the risk–benefit ratio of unfractionated heparin, LMWH generally is the preferred agent for prophylaxis in pregnancy. The need to adjust the LMWH dose according to anti-Xa levels is controversial. The therapeutic range for prophylaxis is uncertain, and dose adjustment to reach target anti-Xa levels has not been shown to increase safety or efficacy of prophylaxis. It is not possible to make definitive recommendations about which prophylactic regimen of unfractionated heparin should be used if active prophylaxis is chosen. All patients with inherited thrombophilias should undergo individualized risk assessment, which may modify management decisions. Various unfractionated heparin and LMWH regimens are described in Table 3.

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

The decision to treat with thromboprophylaxis, anticoagulant therapy, or no pharmacologic treatment (antepartum surveillance) is influenced by the venous thromboembolism history, severity of inherited thrombophilia, and additional risk factors. All patients with inherited thrombophilias should undergo individualized risk assessment, which may modify management decisions. The decision regarding intensity of treatment may be shaped by other

Table 2. How to Test for 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 (<60%)	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. Anticoagulation Regimen Definitions ⇦

Anticoagulation Regimen	Definition
Prophylactic LMWH*	Enoxaparin, 40 mg SC once daily Dalteparin, 5,000 units SC once daily Tinzaparin, 4,500 units SC once daily
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 May target an anti-Xa level in the therapeutic range of 0.6–1.0 units/mL for twice daily regimen; slightly higher doses may be needed for a once-daily regimen.
Minidose prophylactic UFH	UFH, 5,000 units SC every 12 hours
Prophylactic UFH	UFH, 5,000–10,000 units SC every 12 hours 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
Therapeutic UFH†	UFH, 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5–2.5) 6 hours after injection
Postpartum anticoagulation	Prophylactic LMWH/UFH for 4–6 weeks or vitamin K antagonists for 4–6 weeks with a target INR of 2.0–3.0, with initial UFH or LMWH therapy overlap until the INR is 2.0 or more for 2 days
Surveillance	Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep vein thrombosis or pulmonary embolism

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low molecular weight heparin; SC, subcutaneously; UFH, unfractionated heparin.

*Although at extremes of body weight, modification of dose may be required.

†Also referred to as weight adjusted, full treatment dose.

risk factors, such as cesarean delivery, prolonged immobility, obesity, and family history of thrombophilia or venous thromboembolism. Treatment recommendations are listed in Table 4.

For women receiving prolonged anticoagulation therapy for a venous thromboembolism episode who become pregnant, it is recommended that unfractionated heparin or LMWH be used in place of vitamin K antagonists. Low molecular weight heparin is preferred over unfractionated heparin for the prevention and treatment of venous thromboembolism in pregnant women. Any increased risk of venous thromboembolism in pregnancy appears to be greatest before 20 weeks of gestation; therefore, if antepartum prophylaxis is used, it should be initiated in the first trimester. Postpartum treatment levels should be at least equal to antepartum treatment. Because the risk of postpartum thromboembolic events per day is higher than the risk during pregnancy, many experts recommend postpartum prophylaxis in women with low-risk thrombophilias and clinical scenarios in which antepartum thromboprophylaxis is not currently recommended, as indicated in Table 4 (57, 58). Women using warfarin or unfractionated heparin who are breastfeeding can continue taking these medications (59–61). Women using LMWH can continue this thromboprophylaxis, although this recommendation is based on limited evidence. For all women with a previous history of deep vein thrombosis, the use of graduated elastic compression stockings may be considered in the antepartum and postpartum periods (12).

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

The use of pneumatic compression boots or elastic stockings should be considered for patients with a known thrombophilia until they are ambulatory postpartum. In addition, intrapartum prophylaxis with unfractionated heparin should be considered in patients at higher risk.

Regardless of whether the patient is receiving prophylactic, intermediate, or therapeutic doses of LMWH, consideration should be given to substituting a comparable dose of unfractionated heparin at 36 weeks of

Table 4. 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 anticoagulation therapy if the patient has additional risks factors‡
Low-risk thrombophila with a family history (first-degree relative) of VTE	Surveillance without anticoagulation therapy	Postpartum 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 or surveillance without anticoagulation therapy	Postpartum anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ without previous VTE	Surveillance without anticoagulation therapy, or prophylactic LMWH or UFH	Postpartum anticoagulation therapy
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 regimen	Postpartum anticoagulation therapy, or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be at least as high as antepartum treatment)
No thrombophilia with previous single episode of VTE associated with transient risk factor that is no longer present—Excludes pregnancy- or estrogen-related risk factor	Surveillance without anticoagulation therapy	Postpartum anticoagulation therapy‖
No thrombophilia with previous single episode of VTE associated with transient risk factor that was pregnancy- or estrogen-related	Prophylactic-dose LMWH or UFH‖	Postpartum anticoagulation therapy
No thrombophilia with previous single episode of VTE without an associated risk factor (idiopathic)—Not receiving long-term anticoagulation therapy	Prophylactic-dose LMWH or UFH‖	Postpartum anticoagulation therapy
Thrombophilia or no thrombophilia with two or more episodes of VTE—Not receiving long-term anticoagulation therapy	Prophylactic or therapeutic-dose LMWH or Prophylactic or therapeutic-dose UFH	Postpartum anticoagulation therapy or Therapeutic-dose LMWH/UFH for 6 weeks
Thrombophilia or no thrombophilia with two or more episodes of VTE—Receiving long-term anticoagulation therapy	Therapeutic-dose LMWH or UFH	Resumption of long-term anticoagulation therapy

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

*Postpartum treatment levels should be greater or equal to antepartum treatment. Treatment of acute VTE and management of antiphospholipid syndrome are addressed in other Practice Bulletins.

†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 before age 50 years, or other major thrombotic risk factors (eg, obesity or prolonged immobility).

§High-risk thrombophilia: antithrombin deficiency; double heterozygous for prothrombin *G20210A* mutation and factor V Leiden; factor V Leiden homozygous or prothrombin *G20210A* mutation homozygous.

‖Surveillance without anticoagulation therapy is supported as an alternative approach by some experts.

gestation to permit induction of neuroaxial anesthesia during labor and delivery. Alternatively, adjusted-dose subcutaneous LMWH or unfractionated heparin can be discontinued 24–36 hours before an induction of labor or scheduled cesarean delivery to avoid the anticoagulant effect during delivery.

Patients receiving prophylactic anticoagulation therapy should be instructed to withhold their injections at the onset of labor. If vaginal or cesarean delivery occurs more than 4 hours after a prophylactic dose of unfractionated heparin, the patient is not at significant risk of hemorrhagic complications. Beyond 12 hours after a prophylactic dose or 24 hours after a therapeutic dose of LMWH, spinal anesthesia should not be withheld because the risk of procedure-related bleeding is limited (62, 63). Patients receiving unfractionated heparin or LMWH who require rapid reversal of the anticoagulant effect for delivery can be treated with protamine sulfate (64). In addition, antithrombin concentrates can be used in antithrombin-deficient patients in the peripartum period.

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

Postpartum doses of unfractionated heparin or LMWH should be equal to or greater than antepartum therapy. Unfractionated heparin or LMWH can be restarted 4–6 hours after vaginal delivery or 6–12 hours after cesarean delivery. Patients who will be treated with warfarin may begin therapy immediately after delivery. The initial dose of warfarin should be 5 mg daily for 2 days, with subsequent doses determined by monitoring the international normalized ratio. To avoid paradoxical thrombosis and skin necrosis from the early antiprotein C effect of warfarin, women should continue to take therapeutic doses of unfractionated heparin or LMWH for 5 days and until the international normalized ratio is therapeutic (2.0–3.0) for 2 consecutive days. Warfarin, LMWH, 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 (59–61).

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

The risk of venous thromboembolism among women using estrogen-containing oral contraceptives increases 35–99-fold and 16-fold among women heterozygous for factor V Leiden and prothrombin *G20210A* mutations, respectively (65). The annual risk of venous thromboembolism is 5.7 per 10,000 among factor V Leiden carriers, compared with 28.5 per 10,000 among factor V Leiden heterozygous women using estrogen-containing contraceptives (relative risk of 34.7) (66). Therefore, alternative methods, such as intrauterine devices (including those containing progestin), progestin-only pills or implants, and barrier methods, should be considered. However, screening all women for thrombophilias before initiating combination contraception is not recommended (67–69).

Summary of Recommendations

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

- Warfarin, LMWH, 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.
- Testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption is not recommended because it is unclear if anticoagulation therapy reduces recurrence.
- There is insufficient evidence to either screen for or treat women with inherited thrombophilias and obstetric histories that include complications such as fetal growth restriction or preeclampsia.
- 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 for venous thromboembolism, screening with either *MTHFR* mutation analyses or fasting homocysteine levels is not recommended.

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

- Recommended screening tests for inherited thrombophilias should include factor V Leiden mutation; prothrombin *G20210A* mutation; and antithrombin, protein C, and protein S deficiencies.
- Treatment recommendations for women with inherited thrombophilias are listed in Table 4.
- All patients with inherited thrombophilias should undergo individualized risk assessment, which may modify management decisions.

Proposed Performance Measure

Documentation of individual risk assessment for women with known inherited thrombophilias

References

1. Lockwood CJ, Krikun G, Rahman M, Caze R, Buchwalder 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) [PubMed] ⇦
2. Lockwood CJ, Krikun G, Schatz F. The decidua regulates hemostasis in human endometrium. Semin Reprod Endocrinol 1999;17:45–51. (Level III) [PubMed] ⇦
3. Bremme KA. Haemostatic changes in pregnancy. Best Pract Res Clin Haematol 2003;16:153–68. (Level III) [PubMed] ⇦
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) [PubMed] [Full Text] ⇦

5. Hellgren M. Hemostasis during normal pregnancy and puerperium. Semin Thromb Hemost 2003;29:125–30. (Level III) [PubMed] ⇦

6. Gherman RB, Goodwin TM, Leung B, Byrne JD, Hethumumi R, Montoro M. Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy. Obstet Gynecol 1999;94:730–4. (Level II-3) [PubMed] [*Obstetrics & Gynecology*] ⇦

7. Chang J, Elam-Evans LD, Berg CJ, Herndon J, Flowers L, Seed KA, et al. Pregnancy-related mortality surveillance—United States, 1991–1999. Morb Mortal Wkly Rep Surveill Summ 2003;52:1–8. (Level II-3) [PubMed] [Full Text] ⇦

8. Scifres CM, Macones GA. The utility of thrombophilia testing in pregnant women with thrombosis: fact or fiction? Am J Obstet Gynecol 2008;199:344.e1–344.e7. (Level III) [PubMed] [Full Text] ⇦

9. Franco RF, Reitsma PH. Genetic risk factors of venous thrombosis. Hum Genet 2001;109:369–84. (Level III) [PubMed] ⇦

10. 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) [PubMed] [Full Text] ⇦

11. Zotz RB, Gerhardt A, Scharf RE. Inherited thrombophilia and gestational venous thromboembolism. Best Pract Res Clin Haematol 2003;16:243–59. (Level III) [PubMed] ⇦

12. 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. American College of Chest Physicians. Chest 2012;141(suppl):e691S–736S. (Level III) [PubMed] [Full Text] ⇦

13. 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) [PubMed] [Full Text] ⇦

14. 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 [letter]. Thromb Haemost 1990;63:319–20. (Level III) [PubMed] ⇦

15. 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 [letter]. Thromb Haemost 1994;71:799–800. (Level III) [PubMed] ⇦

16. 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) [PubMed] ⇦

17. 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) [PubMed] [Full Text] ⇦

18. Fardella P, Parra M, Conte G, Flores C, Munoz H, Soto L, et al. Free protein S (PS) in normal pregnancy: a comparison between two analytical methods [Spanish]. Rev Med Chil 2005;133:633–8. (Level III) [PubMed] ⇦

19. 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 errata appear in Ann Intern Med 1997;127:1138; Ann Intern Med 1997; 126:835]. Ann Intern Med 1996;125:955–60. (Level II-2) [PubMed] [Full Text] ⇦

20. Carraro P. Guidelines for the laboratory investigation of inherited thrombophilias. Recommendations for the first level clinical laboratories. European Communities Confederation of Clinical Chemistry and Laboratory Medicine, Working Group on Guidelines for Investigation of Disease. Clin Chem Lab Med 2003;41:382–91. (Level III) [PubMed] ⇦

21. Hellgren M, Tengborn L, Abildgaard U. Pregnancy in women with congenital antithrombin III deficiency: experience of treatment with heparin and antithrombin. Gynecol Obstet Invest 1982;14:127–41. (Level III) [PubMed] ⇦

22. 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) [PubMed] ⇦

23. 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) [PubMed] ⇦

24. 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) [PubMed] [Full Text] ⇦

25. 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) [PubMed] ⇦

26. Eichinger S. Homocysteine, vitamin B6 and the risk of recurrent venous thromboembolism. Pathophysiol Haemost Thromb 2003;33:342–4. (Level III) [PubMed] [Full Text] ⇦

27. 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) [PubMed] [Full Text] ⇦

28. 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) [PubMed] [Full Text] ⇦

29. 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) [PubMed] [Full Text] ⇦

30. 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) [PubMed] [Full Text] ⇦

31. 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) [PubMed] ⇦

32. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet 2003;361:901–8. (Meta-analysis) [PubMed] [Full Text] ⇦

33. 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) [PubMed] ⇦

34. 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) [PubMed] [Full Text] ⇦

35. Lissalde-Lavigne G, Fabbro-Peray P, Cochery-Nouvellon E, Mercier E, Ripart-Neveu S, Balducchi 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) [PubMed] [Full Text] ⇦

36. 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) [PubMed] [Full Text] ⇦

37. 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) [PubMed] [*Obstetrics & Gynecology*] ⇦

38. 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) [PubMed] [*Obstetrics & Gynecology*] ⇦

39. 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) [PubMed] [Full Text] ⇦

40. 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) [PubMed] [Full Text] ⇦

41. 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 pre-eclampsia? BJOG 2002;109:191–6. (Level II-2) [PubMed] [Full Text] ⇦

42. 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) [PubMed] [Full Text] ⇦

43. 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) [PubMed] ⇦

44. 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) [PubMed] [Full Text] ⇦

45. 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) [PubMed] ⇦

46. 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) [PubMed] [Full Text] ⇦

47. Lin J, August P. Genetic thrombophilias and preeclampsia: a meta-analysis. Obstet Gynecol 2005;105:182–92. (Meta-analysis) [PubMed] [*Obstetrics & Gynecology*] ⇦

48. 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) [PubMed] [Full Text] ⇦

49. 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) [PubMed] [Full Text] ⇦

50. 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) [PubMed] [Full Text] ⇦

51. 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) [PubMed] [Full Text] ⇦

52. 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) [PubMed] [Full Text] ⇦

53. 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) [PubMed] [Full Text] ⇦

54. 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) [PubMed] ⇦

55. Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows R, Kearon C, Geerts W, Kovacs M, Weitz JI, Robinson KS, Whittom R, Couture G; Recurrence of Clot in This Pregnancy Study Group. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. N Engl J Med. 2000; 343:1439–44. (Level I) [PubMed] [Full Text] ⇦

56. Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD004734. DOI: 10.1002/14651858.CD004734.pub3. (Level III) [PubMed] [Full Text] ⇦

57. 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) [PubMed] [Full Text] ⇦

58. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. 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) [PubMed] [Full Text] ⇦

59. Clark SL, Porter TF, West FG. Coumarin derivatives and breast-feeding. Obstet Gynecol 2000;95:938–40. (Level III) [PubMed] [*Obstetrics & Gynecology*] ⇦

60. 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) [PubMed] [Full Text] ⇦

61. 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) [PubMed] [Full Text] ⇦

62. Duhl AJ, Paidas MJ, Ural SH, Branch W, Casele H, Cox-Gill J, et al. Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. Pregnancy and Thrombosis Working Group. Am J Obstet Gynecol 2007;197:457.e1–457.21. (Level III) [PubMed] [Full Text] ⇦

63. Horlocker TT, Wedel DJ, Benzon H, Brown DL, Enneking FK, Heit JA, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med 2003;28: 172–97. (Level III) [PubMed] ⇦

64. 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) [PubMed] ⇦

65. Gomes MP, Deitcher SR. Risk of venous thromboembolic disease associated with hormonal contraceptives and hormone replacement therapy: a clinical review. Arch Intern Med 2004;164:1965–76. (Level III) [PubMed] [Full Text] ⇦

66. Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet 1994;344:1453–7. (Level II-2) [PubMed] ⇦

67. Use of hormonal contraception in women with coexisting medical conditions. ACOG Practice Bulletin No. 73. American College of Obstetricians and Gynecologists. Obstet Gynecol 2006;107:1453–72. (Level III) [PubMed] [*Obstetrics & Gynecology*] ⇦

68. 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) [PubMed] [Full Text] ⇦

69. Comp PC, Zacur HA. Contraceptive choices in women with coagulation disorders. Am J Obstet Gynecol 1993; 168:1990–3. (Level III) [PubMed] ⇦

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–January 2013. 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.

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