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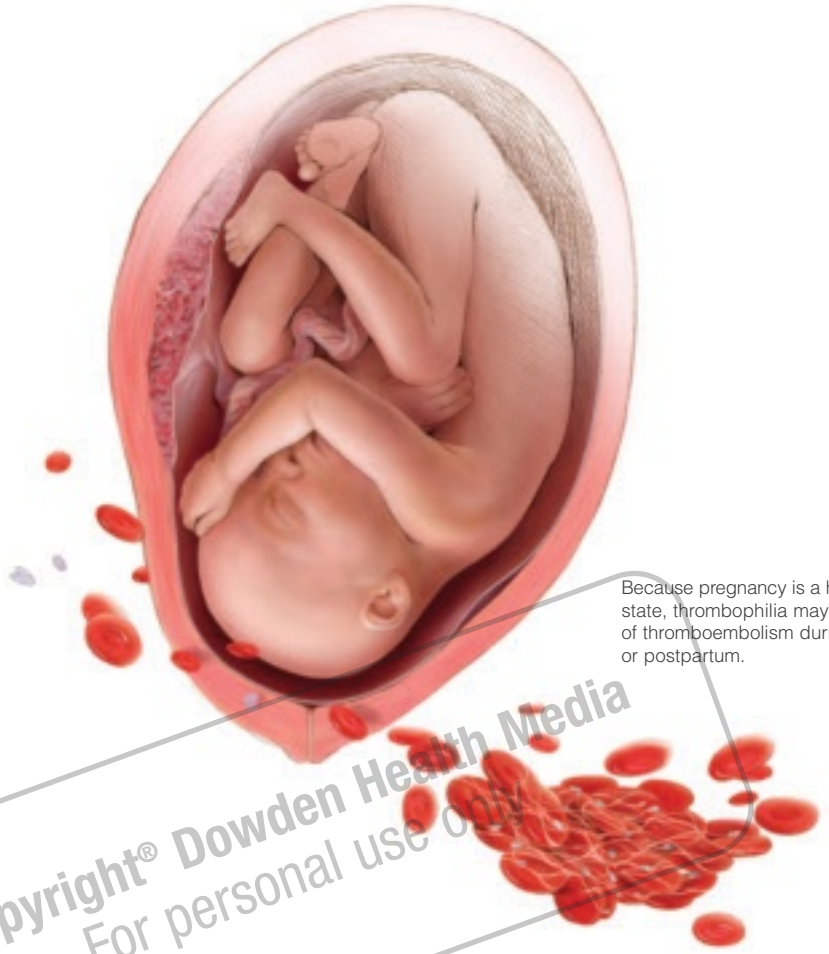

Because pregnancy is a hypercoagulable state, thrombophilia may raise the risk of thromboembolism during gestation or postpartum.

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Thrombophilia in pregnancy: Whom to screen, when to treat

Despite extensive research on testing and prophylaxis, a cautious approach is warranted

IN THIS ARTICLE

Thrombophilia has been widely investigated—and that may be one of the main challenges in detecting and managing it during pregnancy: Numerous studies have yielded different estimates of the incidence of various clotting disorders in pregnancy—itself a hypercoagulable state—and conflicting screening and prevention recommendations. The authors offer whatever recommendations have emerged.

Why thrombophilia matters

During pregnancy, clotting factors I, VII, VIII, IX, and X rise; protein S and fibrinolytic activity diminish; and resistance to activated protein C develops.[1,2] When compounded by thrombophilia—a broad spectrum of coagulation disorders that increase the risk for venous and arterial thrombosis—the hypercoagulable state of pregnancy may increase the risk of thromboembolism during pregnancy or postpartum.[3]

Pulmonary embolism is the leading cause of maternal death in the United States.[1] Concern about this lethal sequela has led to numerous recommendations for screening and subsequent prophylaxis and therapy.

Two types

Thrombophilias are inherited or acquired (**TABLE 1**). The most common inherited disorders during pregnancy are mutations in factor V Leiden, prothrombin gene, and methylenetetrahydrofolate reductase

IMAGE: KIMBERLY MARTENS

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(MTHFR) (**TABLE 2**). Caucasians have a higher rate of genetic thrombophilias than other racial groups.

Antiphospholipid antibody (APA) syndrome is the most common acquired thrombophilia of pregnancy. It can be diagnosed when the immunoglobulin G or immunoglobulin M level is 20 g per liter or higher, when lupus anticoagulant is present, or both.[4]

Link to adverse pregnancy outcomes

During the past 2 decades, several epidemiologic and case-control studies have explored the association between thrombophilias and adverse pregnancy outcomes,[2–6] which include the following maternal effects:

- Venous thromboembolism, including deep vein thrombosis, pulmonary embolism, and cerebral vein thrombosis
- Arterial thrombosis (peripheral, cerebral)
- Severe preeclampsia

Placental and fetal abnormalities include:

- Thrombosis and infarcts
- Abruptio placenta
- Recurrent miscarriage
- Fetal growth restriction
- Death
- Stroke

TABLE 1

Thrombophilias are inherited or acquired

INHERITED
• Protein S deficiency
• Protein C deficiency
• Protein Z deficiency
• Antithrombin III
• Factor V Leiden mutation
• MTHFR mutation
• Homozygosity to MTHFR C677T
• Homozygosity to 4G/4G mutation in PAI-1 gene
• Prothrombin G20210A mutation
• Polymorphisms in thrombomodulin gene
ACQUIRED
• Antiphospholipid antibody syndrome
– Lupus anticoagulant
– Anticardiolipin antibodies
– Activated protein C resistance
• Hyperhomocysteinemia

MTHFR = methylenetetrahydrofolate reductase

Preeclampsia and thrombophilia

The association between preeclampsia and thrombophilia remains somewhat unclear because of inconsistent data. Because of this, we do not recommend routine screening for thrombophilia in women with preeclampsia.

An association between inherited thrombophilias and preeclampsia was reported by Dekker et al in 1995.[7] Since then, numerous retrospective and case-controlled studies have assessed the incidence of thrombophilia in women with severe preeclampsia.[7–25] Their findings range from:

- Factor V Leiden: 3.7% to 26.5%
- Prothrombin gene mutation: 0 to 10.8%
- Protein S deficiency: 0.7% to 24.7%
- MTHFR variant: 6.7% to 24.0%

A meta-analysis of all case-controlled studies suggests that factor V Leiden is the only thrombophilia associated with an increased risk of preeclampsia.[5] However, almost all studies included in this analysis involved women with severe preeclampsia who were referred to a tertiary-care obstetric center, whereas women in the control groups had a normal term pregnancy. These studies were therefore subject to selection bias because they overestimated the rate of thrombophilias in study groups and underestimated it in control groups.

Other points of contention are the varying levels of severity of preeclampsia and of gestational age at delivery, as well as racial differences. For example, most studies found an association between thrombophilia and severe preeclampsia at less than 34 weeks' gestation, but not between

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Antiphospholipid antibody syndrome is the most common acquired thrombophilia of pregnancy

TABLE 2

Prevalence of thrombophilias in women with normal pregnancy outcomes

THROMBOPHILIA	PREVALENCE (%)
Factor V Leiden mutation	2–10
MTHFR mutation	8–16
Prothrombin gene mutation	2–6
Protein C and S deficiencies	0.2–1.0*
Anticardiolipin antibodies	1–7

* Combined rate
MTHFR = methylenetetrahydrofolate reductase

thrombophilia and mild preeclampsia at term. In addition, a recent prospective observational study at multiple centers involving 5,168 women found a factor V Leiden mutation rate of 6% among white women, 2.3% among Asians, 1.6% in Hispanics, and 0.8% in African Americans.[8] This large study found no association between thrombophilia and preeclampsia in these women. Therefore, based on available data, we do not recommend routine screening for factor V Leiden in women with severe preeclampsia.

Preeclampsia and APA syndrome

In 1989, Branch et al[26] first reported an association between APA syndrome and severe preeclampsia at less than 34 weeks' gestation. They recommended that women with severe preeclampsia at this gestational age be screened for APA syndrome and treated when the screen is positive. Several later studies supported or refuted the association between APA syndrome and preeclampsia,[26,27] and a recent report concluded that routine testing for APA syndrome in women with early-onset preeclampsia is unwarranted.[26] Therefore, we do not recommend routine screening for APA in women with severe preeclampsia.

No need to screen women with abruptio placenta

The placental circulation is comparable to venous circulation, with low pressure and low flow velocity rendering it susceptible to thrombotic complications at the maternal–placental interface and consequent premature separation of the placenta.

It is difficult to confirm an association between thrombophilia and abruptio placenta because of confounding variables such as chronic hypertension, cigarette and cocaine use, and advanced maternal age.[3] Studies reviewing this association are scarce, and screening for thrombophilia is discouraged in pregnancies marked by abruptio placenta.

Kupferminc et al[28] found that 25%, 20%, and 15% of thrombophilia patients with placental abruption had mutations in factor V Leiden, prothrombin gene, and MTHFR, respectively. In contrast, Prochazka et al[29] found 15.7% of their cohort of patients with abruptio placenta to have factor V Leiden mutation.

A large prospective, observational study of more than 5,000 asymptomatic pregnant women at multiple centers found no association between abruptio placenta and factor V Leiden mutation.[8] Nor were there cases of abruptio placenta among 134 women who were heterozygous for factor V Leiden.

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A study of >5,000 asymptomatic gravidas found no association between abruptio placenta and factor V Leiden mutation

And no routine screening in cases of IUGR

Routine screening for thrombophilias in women with intrauterine growth restriction (IUGR) is not recommended. One reason: The prevalence of thrombophilias in these women ranges widely, depending on the study cited: from 2.8% to 35% for factor V Leiden and 2.8% to 15.4% for prothrombin gene mutation (**TABLE 3**). In addition, in contrast to earlier studies, a large case-control trial by Infante-Rivard et al[30] found no increased risk of IUGR in women with thrombophilias, except for a subgroup of women with the MTHFR variant who did not take a prenatal multivitamin.

A recent meta-analysis of case-control studies by Howley et al[31] found a significant association between factor V Leiden, the prothrombin gene variant, and IUGR, but the investigators cautioned that this

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TABLE 3

Incidence of thrombophilias in women with intrauterine growth restriction

STUDY	FACTOR V LEIDEN (%)		PROTHROMBIN GENE MUTATION (%)	
	IUGR	CONTROLS	IUGR	CONTROLS
Kupferminc et al[50]	5/44 (11.4)	7/110 (6.4)	5/44 (11.4)	3/110 (2.7)
Infante-Rivard et al[30]	22/488 (4.5)	18/470 (3.8)	12/488 (2.5)	11/470 (2.3)
Verspyck et al[51]	4/97 (4.1)	1/97 (1)	3/97 (3.1)	1/97 (1)
McCowan et al[52]	4/145 (2.8)	11/290 (3.8)	4/145 (2.8)	9/290 (3.1)
Dizon-Townson et al*[10]	6/134 (4.5)	233/4,753 (4.9)	NR	NR
Kupferminc**[34]	9/26 (35)	2/52 (3.8)	4/26 (15.4)	2/52 (3.8)

* <5th percentile
** Mid-trimester severe intrauterine growth restriction
IUGR = intrauterine growth restriction, NR = not recorded
SOURCE: Adapted from Clin Obstet Gynecol. 2006;49:850–860

TABLE 4

Incidence of factor V Leiden mutation in women with recurrent pregnancy loss

STUDY	PATIENT SELECTION	PATIENTS (%)	CONTROLS (%)	ODDS RATIO	95% CONFIDENCE INTERVAL
Grandone et al[53]	≥2 unexplained fetal losses, other causes excluded	7/43 (16.3)	5/118 (4.2)	4.4	1.3–14.7
Ridker et al[54]	Recurrent, spontaneous abortion, other causes not excluded	9/113 (8)	16/437 (3.7)	2.3	1.0–5.2
Sarig et al[55]	≥3 first- or second-trimester losses or ≥1 intrauterine fetal demise, other causes excluded*	96/145 (66)	41/145 (28)	5.0	3.0–8.5

* Excluded chromosomal abnormalities, infections, anatomic alterations, and endocrine dysfunction

strong association may be driven by small, poor-quality studies that yield extreme associations. A multicenter observational study by Dizon-Townson et al[8] found no association between thrombophilia and IUGR in asymptomatic gravidas.

Fetal loss is a complication of thrombophilia

One in 10 pregnancies ends in early death of the fetus (before 20 weeks), and 1 in 200 gestations ends in late fetal loss.[32] When fetal loss occurs in the second and third trimesters, it is due to excessive thrombosis of the placental vessels, placental infarction, and secondary uteroplacental insufficiency.[2,33] Women who are carriers of factor V or prothrombin gene mutations are at higher risk of late fetal loss than noncarriers are (**TABLE 4**).

Fetal loss is a well-established complication in women with thrombophilia, but not all thrombophilias are associated with fetal loss, according to a meta-analysis of 31 studies.[33] In women with thrombophilia, first-trimester loss is generally associat-

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Carriers of factor V or prothrombin gene mutations are at higher risk of late fetal loss than noncarriers are

TABLE 5

How women with a previous adverse outcome fare on anticoagulation therapy

STUDY	PATIENTS	PREVIOUS ADVERSE PREGNANCY OUTCOME	ANTICOAGULANT	OUTCOME IN CURRENT PREGNANCY
Riyazi et al[9]	26	Uteroplacental insufficiency	LMWH and low-dose aspirin	Decreased recurrence of preeclampsia (85% to 38%) and IUGR (54% to 15%)
Brenner[37]	50	≥3 first-trimester recurrent pregnancy losses with thrombophilia	LMWH	Higher live birth rate compared with historical controls (75% vs 20%)
Ogueh et al[48]	24	Previous adverse pregnancy outcome plus history of thromboembolic disease, family history of thrombophilia	UFH	No significant improvement
Kupferminc et al[38]	33	Thrombophilia with history of preeclampsia or IUGR	LMWH and low-dose aspirin	With treatment, 3% recurrence of preeclampsia
Grandone et al[53]	25	Repeated pregnancy loss, gestational hypertension, HELLP, or IUGR	UFH or LMWH	90.3% treated with LMWH had good obstetric outcome
Paidas et al[3]	158	Fetal loss, IUGR, placental abruption, or preeclampsia	UFH or LMWH	80% reduction in risk of adverse pregnancy outcome, compared with historical controls (OR, 0.21; 95% CI, 0.11–0.39)

HELLP = hemolysis, elevated liver enzymes, and low platelets; IUGR = intrauterine growth restriction; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin
SOURCE: Adapted from Am J Perinatol. 2006;23:499–506

ed with factor V Leiden, prothrombin gene mutation, and activated protein C resistance. Late, nonrecurrent fetal loss is associated with factor V Leiden, prothrombin gene mutation, and protein S deficiency.[33]

History of adverse outcomes? Offer screening

It is well established that women with a history of fetal death, severe preeclampsia, IUGR, abruptio placenta, or recurrent miscarriage have an increased risk of recurrence in subsequent pregnancies.[3,30,34-36] The rate of recurrence of any of these outcomes may be as high as 46% with a history of 2 or more adverse outcomes, even before any thrombophilia is taken into account.[3] Although there are few studies describing the rate of recurrence of adverse pregnancy outcomes in women with thrombophilia and a previous adverse outcome (**TABLE 5**), it appears to range from 66% to 83% in untreated women.[3,37]

Based on these findings, some authors recommend screening for thrombophilia in women who have had adverse pregnancy outcomes[3,9,38] and prophylactic therapy in subsequent pregnancies when the test is positive. Therapy includes low-dose aspirin with or without subcutaneous heparin, as well as folic acid and vitamin B_6 supplements, according to the type of

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Screen women with a prior adverse pregnancy outcome for thrombophilia; without treatment, their risk of another adverse outcome ranges from 66% to 83%

TABLE 6
Risk of thromboembolism during pregnancy and postpartum in women with thrombophilia

THROMBOPHILIA	RISK (%)	
	ASYMPTOMATIC WOMEN	HISTORY OF VENOUS THROMBOEMBOLISM
Factor V Leiden		
Heterozygous	0.2	10
Homozygous	1–2	15–20
Prothrombin gene mutation		
Heterozygous	0.5	10
Homozygous	2.3	20
Factor V Leiden and prothrombin gene mutation	5	20
Antithrombin deficiency	7	40
Protein C deficiency	0.5	5–15
Protein S deficiency	0.1	Unknown

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The risk of VTE during pregnancy and postpartum for women who have antithrombin deficiency and a history of VTE is roughly 40%

thrombophilia present as well as the nature of the previous adverse outcome.

No randomized trials on prophylaxis

We lack randomized trials evaluating thromboprophylaxis for prevention of recurrent adverse pregnancy outcomes in women with previous severe preeclampsia, IUGR, or abruptio placenta in association with genetic thrombophilia. Therefore, any recommendation to treat such women with low-molecular-weight heparin with or without low-dose aspirin in subsequent pregnancies should remain empiric and/or prescribed after appropriate counseling of the patients regarding risks and benefits.

TABLE 6 summarizes the risk of thromboembolism in women with thrombophilia—both for asymptomatic patients and for those with a history of thromboembolism. These percentages should be used when counseling women about their risk and determining management and therapy.

Prophylaxis for APA syndrome and recurrent pregnancy loss

Several randomized trials have described the use of low-dose aspirin and heparin in women with APA syndrome and a history of recurrent pregnancy loss, although the results are inconsistent (**TABLE 7**).[39–45] The inconsistency may be due to varying definitions of APA syndrome and gestational age at the time of randomization, as well as the population studied (previous thromboembolism, presence or absence of lupus anticoagulant, level of titer of anticardiolipin antibodies, presence or absence of previous stillbirth). Nevertheless, we recommend that women with true APA syndrome (presence of lupus anticoagulant, high titers of immunoglobulin G, history of thromboembolism or recurrent stillbirth) receive prophylaxis with low-dose aspirin, with subcutaneous heparin added once fetal cardiac activity is documented.[46]

Genetic thrombophilias

Few published studies describe prophylactic use of low-molecular-weight heparin with or without low-dose aspirin in women with genetic thrombophilia and a history of adverse pregnancy outcomes. All but 1 of these studies are observational, comparing outcome in the treated pregnancy with that of previously untreated gestations in the same woman.[3,9,38,44,45,47] These studies included a limited number of women and a heterogeneous group of patients with various thrombophilias; they also involved different therapies (**TABLE 7**).[3,9,38,41,48,49]

Gris et al[47] performed a randomized trial in 160 women with at least 1 prior fetal loss after 10 weeks' gestation who were heterozygous for factor V Leiden or prothrombin G20210A mutation, or had protein S deficiency. Beginning at 8 weeks' gestation, these women were assigned to treatment with 40 mg of enoxaparin (n = 80) or 100 mg of low-dose aspirin (n = 80) daily. All women also received 5 mg of folic acid daily.

In the women treated with enoxaparin, 69 (86%) had a live birth, compared with 23 (29%) women treated with low-dose aspirin. The women treated with enoxaparin also had significantly higher median neonatal birth weights and a lower rate of IUGR (10% versus 30%). The authors concluded that women with factor

TABLE 7

Live births in women with APA and a history of fetal loss

STUDY	TREATMENT	CONTROL	NO. OF LIVE BIRTHS (%)	
			TREATED WOMEN	CONTROL GROUP
Cowchock et al[39]	Aspirin/heparin	Aspirin/prednisone	9/12 (75)	6/8 (75)
Laskin et al[40]	Aspirin/prednisone	Placebo	25/42 (60)	24/46 (52)
Kutteh[41]	Aspirin/heparin	Aspirin only	20/25 (80)	11/25 (44)
Rai et al[42]	Aspirin/heparin	Aspirin only	32/45 (71)	19/45 (42)
Silver et al[43]	Aspirin/prednisone	Aspirin only	12/12 (100)	22/22 (100)
Pattison et al[44]	Aspirin	Placebo	16/20 (80)	17/20 (85)
Farquharson et al[45]	Aspirin/LMWH	Aspirin only	40/51 (78)	34/47 (72)

LMWH = low-molecular-weight heparin

V Leiden, prothrombin gene mutation, or protein S deficiency and a history of fetal loss should receive enoxaparin prophylaxis in subsequent pregnancies.

History of severe preeclampsia, IUGR, or abruptio placenta. No randomized trials have evaluated thromboprophylaxis in women with this history who have genetic thrombophilia. For this reason, any recommendation to treat these women with low-molecular-weight heparin with or without low-dose aspirin in subsequent pregnancies remains empiric. Prophylaxis can be prescribed after an appropriate discussion of risks and benefits with the patient.

Unresolved questions keep management experimental

What is the likelihood that a woman carrying a gene mutation that predisposes her to thrombophilia will have a serious complication during pregnancy? And how safe and effective is prophylaxis?

There is a prevailing need for a double-blind placebo-controlled trial to address these questions and evaluate the benefit of heparin in pregnant women with a history of adverse pregnancy outcomes and thrombophilia. Until then, screening and treatment for thrombophilia remain experimental in these women. ■

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Proceed in the half-dark: Your care of the thrombophilic pregnant woman is not yet illuminated by rigorous clinical trials

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