Prenatal Screening for Thrombophilias: Indications and Controversies

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KEYWORDS

• Thrombophilia • Inherited thrombophilia
• Acquired thrombophilia • Pregnancy
• Venous • Thromboembolism

Pregnancy is considered to be a hypercoagulable state and encompasses all 3 elements of Virchow's triad. There are numerous physiologic changes in pregnancy to account for this hypercoagulable state. In pregnancy, there is an increase in fibrinogen, von Willebrand factor, and clotting Factors II, VII, VIII, IX, and X.[1,2] There is a decrease in physiologic anticoagulants manifested by a decrease in protein S (PS) and an increase in protein C (PC) resistance. There are decreases in fibrinolytic activity, increased venous stasis, and vascular injury associated with delivery. Pregnancy is associated with increased clotting potential, decreased anticoagulant activity, and decreased fibrinolyis.[3,4]

A thrombophilia is defined as a disorder of hemostasis that predisposes a person to a thrombotic event.[5] Data suggest that at least 50% of cases of venous thromboembolism[6] in pregnant women are associated with an inherited or acquired thrombophilia.[7,8] Inherited and acquired thrombophilias can lead to an increased risk of maternal thromboembolism and adverse pregnancy outcomes such as recurrent pregnancy loss, intrauterine fetal demise (IUFD), preterm preeclampsia, and intrauterine growth restriction (IUGR). Thrombophilias have been associated with an increased risk of maternal and perinatal morbidity and mortality. Sometimes inherited and acquired thrombophilias are used interchangeably, which is a misconception. Inherited and acquired thrombophilias have different indications for testing. It is important as a clinician to identify what patient is at risk, what are the indications for testing, what laboratory testing should be performed, and what patient should receive

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treatment. It is best for the clinician to perform a thrombophilia workup preconceptually because thrombophilia manifestations can start in early pregnancy.

INHERITED THROMBOPHILIAS

Inherited thrombophilias result from deficiencies from components of the coagulation system. Inherited thrombophilias have been associated with venous thromboembolism (VTE) and adverse pregnancy outcomes. Included in the category of inherited thrombophilias are factor V Leiden (FVL) mutation, prothrombin (PT) gene (G20210A) mutation, antithrombin (AT) deficiency, PC deficiency, PS deficiency, and hyperhomocysteinemia.

Factor V Leiden

FVL mutation is the most common inherited thrombophilia and is present in about 5% to 9% of the white European population (**Table 1**).[9] FVL mutation is inherited in an autosomal dominant fashion and arises from a point mutation where glutamine is substituted for an arginine at position 506. This amino acid substitution impairs PC and PS activity; therefore, FVL is the leading case of activated PC resistance. Screening can be performed by assessing activated PC (aPC) resistance using a second-generation coagulation assay followed by genotyping for the FVL mutation. Alternatively, patients can simply be genotyped for FVL.[3] FVL can be accurately diagnosed in pregnancy.

Prothrombin Gene (G20210A) Mutation

PT gene mutation is present in 2% to 3% of the white European population (see **Table 1**).[10] PT gene mutation occurs due to a point mutation causing a guanine to adenine substitution at nucleotide position 20210. Polymerase chain reaction (PCR) methods have been used to detect the G20210A PT gene mutation in genomic DNA.[10,11] Prothrombin gene mutation is associated with elevated plasma levels of PT, but it should not be used for screening.[10–12] Prothrombin gene mutation can be tested in the setting of pregnancy.

AT Deficiency

AT deficiency is present in 0.02% to 0.2% of the population, and is the most thrombogenic of the inherited thrombophilias (see **Table 1**).[2,9] AT III has a 70% to 90% lifetime risk of thromboembolism.[13] Deficiencies in AT III result from numerous point mutations, deletions, and insertions, and are usually inherited in an autosomal dominant fashion.[14] Although AT is most often inherited, it can also be acquired due to liver

Table 1
Risk of VTE with inherited thrombophilias

Thrombophilia	Population Frequency in Caucasians	Frequency of VTE in Asymptomatic Pregnancies	Frequency of VTE in Symptomatic Pregnancies
FVL	5%–9%[9]	0.26%[40]	10%–17%[40]
G20210A PT	2%–3%[10]	0.37%[40]	16.9%[11]
AT	0.02–0.2%[9]	7.2%[40]	60%[41]
PC	0.2–0.5%[17,18]	0.18%[40]	2%–17%[40]
PS	0.03–0.13%[22]	0.8%[40]	0%–22%[40]

Symptomatic pregnancy includes personal and/or family history of VTE.

failure, increased consumption secondary to disseminated intravascular coagulation and/or sepsis, or increased renal excretion in severe nephritic syndrome. AT deficiency is diagnosed with an AT-heparin cofactor assay. This assay will detect all currently recognized subtypes of familial AT deficiency and is therefore the best single laboratory screening test for this disorder. AT deficiency should not be screened for in the setting of pregnancy, acute thrombosis, or during anticoagulation.

Hyperhomocysteinemia

Hyperhomocysteinemia can be seen with deficiencies in vitamins B6, B12, folic acid, and methylenehydrofolate reductase (MTHFR). Normal circulating plasma levels of homocysteine range from 5 to 16 μmol/L. Hyperhomocysteinemia can be diagnosed with fasting homocysteine levels and can further be classified as severe (>100 μmol/L), moderate (25–100 μmol/L), and mild (16–24 μmol/L).[9] MTHFR can be a cause of mild to severe hyperhomocysteinemia. Frosst and colleagues[15] explained the thermolability of MTHFR and how the mechanism was caused by a cytosine to thymine substitution at base pair 677 in the MTHFR gene.[16] Homozygosity for MTHFR is a relatively common cause of mildly elevated plasma homocysteine levels in the general population, often occurring in association with low serum folate levels.

Protein C

PC deficiency is present in 0.2% to 0.5% of the general population (see **Table 1**).[17,18] Heterozygous PC deficiency is inherited in an autosomal dominant pattern. Most affected patients are heterozygous with the plasma PC concentration being approximately 50% of normal in both immunologic and functional assays. PC is a vitamin K–dependent protein synthesized in the liver. The gene for PC is located on chromosome 2 (2q13–14).[19,20] PC circulates as a zymogen and exerts its anticoagulant function after activation to the serine protease, aPC. The primary effect of aPC is to inactivate coagulation factors Va and VIIIa, which are necessary for efficient thrombin generation and factor X activation.[21] The inhibitory effect of aPC is markedly enhanced by PS, another vitamin K–dependent protein. PC is affected by pregnancy therefore should be tested for preconceptually.

Protein S

PS deficiency is present in 0.03% to 0.13% of the general population (see **Table 1**).[22] PS deficiency is inherited predominately in an autosomal dominant pattern. The gene for PS is located on chromosome 3.[23,24] PS is a vitamin K–dependent glycoprotein and is a cofactor to PC. In the presence of PS, aPC inactivates factors Va and VIIIa, resulting in reduced thrombin generation.[25] Type I is the classical type of PS deficiency and is associated with 50% of the normal total S antigen level, marked reductions in free PS antigen, and reduced PS functional activity.[26–28] There are assays available to measure plasma total and free PS antigen and PS function. Measurement of free PS concentration is the preferred screening test.[29] Patients with levels of total or free PS antigen less than 65 IU/dL are considered to be deficient.[30] PS deficiency should be tested for outside of pregnancy.

ACQUIRED THROMBOPHILIAS

Antiphospholipid Antibody Syndrome (APLS)

APLS is considered to be an acquired thrombophilia, and can be primary or secondary. Primary APLS refers to patients with no other underlying autoimmune disorder. Secondary APLS occurs in the setting of an underlying autoimmune disorder such as systemic lupus erythematosus.[31] APLS is an autoimmune disorder defined by

the presence of characteristic clinical features and specified levels of circulating antiphospholipid antibodies. The combination of VTE and/or adverse obstetric outcomes, and antiphospholipid antibodies encompass this syndrome. The international consensus statement for APLS states that a patient must have one clinical criterion and one laboratory criterion to make the diagnosis.[32]

The clinical criteria for APLS testing can be separated into 2 categories: obstetric outcomes and thrombosis. Obstetric criteria are 3 or more consecutive euploid spontaneous abortions before the 10th week of gestation, unexplained fetal deaths in one or more morphologically normal fetus at 10 weeks or later, and preterm delivery at less than or equal to 34 weeks' gestation resulting from severe preeclampsia or placental insufficiency.[29] Encompassed in the category of placental insufficiency is nonreassuring fetal testing suggestive of fetal hypoxemia, abnormal umbilical Doppler flow velocimetry, oligohydramnios (amniotic fluid index $\leq$5 cm), or birth weight less than 10th percentile (IUGR) requiring delivery at 34 weeks' gestation. There is no actual universal definition of placental insufficiency, nor are there any characteristic placental abnormalities seen on pathology. The criterion for thrombosis is one or more clinical episodes of arterial, venous, or small-vessel thrombosis, in any tissue or organ.[32]

Once clinical criteria are met, antiphospholipid antibody testing should be performed to establish laboratory criteria. Patients should be tested for lupus anticoagulant, anticardiolipin antibody, and anti-β_2-glycoprotein-1 antibody. If any of these laboratory criteria are positive, a confirmatory test must be performed in 12 weeks.[32]

Antiphospholipid Antibodies

Lupus anticoagulants are antibodies directed against plasma proteins that bind to anionic or hexagonal phase phospholipids.[33,34] Lupus anticoagulants paradoxically block phospholipid-dependent clotting assays by interfering with the assembly of the PT complex. Because there are other inhibitors and analytical variables that can cause abnormal test results, several different tests are used to confirm the presence of a lupus anticoagulant. Typically these may include partial thromboplastin time, prothrombin time, dilute or modified Russell viper venom screen (dRVVT or MRVVT), and a hexagonal (II) phase phospholipid assay (Staclot-LA test) or kaolin clotting time. Regardless of the assay used, the result will be reported as present or absent. If the lupus anticoagulant is present, testing must be repeated in 12 weeks to establish if lupus anticoagulant is transient or chronic.

Anticardiolipin antibodies react to the complex of negatively charged phospholipids. These antibodies are detected using conventional immunoassays using purified cardiolipin as the phospholipid matrix. Anticardiolipin antibodies IgG or IgM must be present in medium to high titers of greater than 40 GPL/MPL (IgG/IgM phospholipid) units. Antibodies may be transient, so the testing must be repeated again in 12 weeks for confirmation.

Anti-β_2-glycoprotein-1 is a phospholipid-dependent inhibitor of coagulation. These antibodies are measured by standardized enzyme-linked immunosorbent assay. Antibodies IgG and IgM must have titers greater than the 99th percentile to be considered positive. Like lupus anticoagulant and anticardiolipin antibodies, titers must be tested for again 12 weeks from the first sample. Antiphospholipid antibodies can be tested for during pregnancy.

HISTORY OF VTE

Data suggest that approximately 50% of cases of VTE in pregnant women are associated with an inherited or acquired thrombophilia[7,8]; however, the incidence of VTE is

low, estimated at 0.76 to 1.72 per 1000 pregnancies.[35,36] Due to the low incidence of VTE in pregnancy, universal screening of pregnant women is not cost effective nor is it indicated. All patients with a personal history of venous thrombosis, regardless of thrombophilia status, are prone to recurrent thromboses for many years after the first incident.

APLS has been associated with VTE, arterial thrombosis, stroke, amaurois fugax, and transient ischemic attacks. VTE accounts for 32% of APLS-associated clinical events,[37,38] and up to 25% of thrombotic events occur during pregnancy or the postpartum period.[39]

FVL gene mutation is seen in 40% of patients presenting with a VTE in pregnancy.[10] The probability of VTE in FVL heterozygotes and homozygotes with a personal or family history of VTE is 10% to 17% (see **Table 1**).[40] Prothrombin gene mutation is associated with 16.9% of VTE in pregnancy (see **Table 1**).[10] The relative risk of VTE in pregnancy with PT gene mutation is 15.2 (95% confidence interval 4.2–52.6).[10] Patients with severe deficiencies of AT, PC, and PS are associated with increased risk of VTE in pregnancy and the postpartum period. Seligsohn and Lubetsky[41] found that venous thrombosis occurred during pregnancy and the puerperium in up to 60% of women with an antithrombin deficiency and in up to 20% of women with a deficiency of either PC or PS.[13,37] A case-control study showed that in 129 asymptomatic female relatives of patients with a deficiency of antithrombin, PC, or PS, those who also had a deficiency of one of these proteins had a risk of venous thrombosis during pregnancy and the puerperium that was 8 times as high as the risk in those without a deficiency.[41] Robertson and colleagues[42] found that all heritable thrombophilias, with the exception of MTHFR, were found to be significantly associated with an increased risk of VTE.

MTHFR is associated with decreased enzyme activity and mild hyperhomocysteinemia, and is the most common cause of hyperhomocysteinemia.[16,43] There have been several published studies that have shown an increased relative risk for venous thrombosis with elevated homocysteine levels. Meta-analysis of prospective and retrospective studies demonstrated an association of homocysteine with venous thrombosis.[44] This finding supports the hypothesis that MTHFR can be associated with VTE. However, there are also negative studies that have shown no increased risk of VTE in women with MTHFR and with elevated homocysteine levels with history of VTE.[16,45,46] The VITRO study, a randomized placebo-controlled trial of supplementation with folic acid, pyridoxine, and vitamin B12 in patients with elevated homocysteine levels, showed that supplementation with B vitamins lowers homocysteine values but does not show a risk reduction in recurrent venous thrombosis.[47] If hyperhomocysteinemia is indeed a risk factor for VTE, then lowering the levels should be associated with a reduced risk. In the VITRO study there was no difference in recurrence risk of VTE between the treated group and the placebo group.

KNOWN THROMBOPHILIA WITH NO HISTORY OF VTE

There is some controversy among practitioners of how patients with an incidental finding of thrombophilia without a personal history of VTE should be treated. Venous thromboembolism is a multifactorial disorder in which acquired and genetic risk factors can interact dynamically.[8,40] There are no prospective data examining the risks and benefits of prophylactic anticoagulation in this patient population who have no history of VTE or adverse pregnancy outcome but who test positive for a thrombophilia. The probability of VTE in patients without a history is 0.26% for FVL heterozygote, 1.5% for FVL homozygote, 0.37% for PT carrier, and 4.7% for compound

heterozygosity. The probability of thrombosis with antithrombin deficiency and PC deficiency is 7.2% and 0.8%, respectively.[40] Friederich and colleagues[48] studied 129 asymptomatic female relatives of patients with a deficiency of antithrombin, PC, or PS. Those subjects who also had a deficiency of one of these proteins had a risk of venous thrombosis during pregnancy and the puerperium that was 8 times as high as the risk in those without a deficiency. Patients who are incidentally found to have antiphospholipid antibodies have a risk of thrombosis of less than 1% each year,[37,49] and currently there is no evidence to recommend thromboprophylaxis.

ADVERSE PREGNANCY OUTCOMES

Many agree that patients with a personal history of VTE should be tested for thrombophilias, but controversy arises on what tests should be performed on patients with adverse pregnancy outcomes.

Pregnancy Loss

Pregnancy loss can be separated into 2 categories: recurrent early pregnancy loss (>3 before 10 weeks' gestation) and late fetal loss ($\geq$1 loss after 10 weeks). APLS is associated with both recurrent early pregnancy loss (<10 weeks) and late fetal loss.[48] A greater proportion of pregnancy losses related to antiphospholipid antibodies are second or third trimester fetal deaths.[50] There have been 3 randomized control trials examining the effect of treatment of APLS patients with recurrent pregnancy loss with low-dose aspirin (acetylsalicylic acid; ASA) alone or low-dose ASA plus heparin.[51–53] Two of these studies showed a significantly better pregnancy outcome and higher rate of live births in women with APLS and recurrent pregnancy loss: 71% to 80% with use of heparin and ASA versus 42% to 72% with ASA alone.[51,52] The study by Farquharson and colleagues[53] did not show an improved outcome; however, the patients in this study did not meet laboratory criteria for the diagnosis for APLS.

There is some controversy about whether patients with recurrent or late pregnancy loss should be tested for inherited thrombophilias. Alfirevic and colleagues[54] performed a systematic review and found that unexplained stillbirth, when compared with controls, was more often associated with heterozygous FVL mutation, PS deficiency, and aPC resistance. A meta-analysis by Rey and colleagues[55] showed that FVL, PT gene mutation, and PS deficiency were associated with recurrent early pregnancy loss and late fetal loss. MTHFR, PC, and antithrombin deficiencies were not significantly associated with fetal loss. Kovalevsky and colleagues[56] performed a systematic review on published case-control studies. The combined odds ratios for the association between recurrent pregnancy loss and FVL and PT gene mutation were 2.0 (95% confidence interval 1.5–2.7; P<.001) and 2.0 (95% confidence interval 1.0–4.0; P = .03), respectively. Lissalde-Lavigne and colleagues[57] performed a case-control study nested in a cohort of 32,683 women, and found that patients with FVL and PT gene mutation were more likely to have a pregnancy loss after 10 weeks' gestation. Contrary to other studies, Roque and colleagues[58] examined a cohort of 491 patients with a history of adverse pregnancy outcomes and evaluated the cohort for acquired and inherited thrombophilias. This study showed the presence of one maternal thrombophilia, or more than one thrombophilia were found to be protective of recurrent losses at less than10 weeks (1 thrombophilia: odds ratio 0.55, 95% confidence interval 0.33–0.92; >1 thrombophilia: odds ratio 0.48, 95% confidence interval 0.29–0.78). In contrast, the presence of maternal thrombophilia(s) was modestly associated with an increased risk of losses at greater than 10 weeks (1 thrombophilia: odds

ratio 1.76, 95% confidence interval 1.05–2.94; >1 thrombophilia: odds ratio 1.66, 95% confidence interval 1.03–2.68).[58]

There is only one prospective trial that has studied patients with a history of unexplained pregnancy loss and known inherited thrombophilia. Patients were randomized to receive low-dose ASA or low molecular weight heparin (LMWH). There was a significantly higher number of live births in patients treated with LMWH versus low-dose ASA (odds ratio 15.5, 95% confidence interval 7–34; $P<.0001$).[59] Although this study was not blinded and had no placebo arm, it is the only one looking at possible treatment for history of fetal loss. This positive study can support the argument of testing patients with a history of fetal loss at greater than 10 weeks' gestation for inherited as well as acquired thrombophilias.

Severe Preeclampsia

The association of severe preeclampsia and thrombophilias is controversial. Branch and colleagues[60] performed an observational study and showed that 50% women with APLS developed preeclampsia despite treatment while 25% had severe preeclampsia.[31] A meta-analysis by Robertson and colleagues[42] showed the risk of preeclampsia was significantly associated with heterozygous FVL (odds ratio 2.19; 95% confidence interval 1.46–3.27), heterozygous PT (odds ratio 2.54; 95% confidence interval 1.52–4.23), MTHFR homozygosity (odds ratio 1.37; 95% confidence interval 1.07–1.76), anticardiolipin antibodies (odds ratio 2.73; 95% confidence interval 1.65–4.51), and hyperhomocysteinemia (odds ratio 3.49, 95% confidence interval 1.21–10.11). However, when restricting the analysis to severe preeclampsia only, an odds ratio of 2.04 (95% confidence interval 1.23–3.36) was obtained. Meta-analysis by Alfirevic and colleagues[54] showed that women with preeclampsia/eclampsia were more likely to have heterozygous FVL mutation, heterozygous G20210A PT gene mutation, homozygous MTHFR C677 T mutation, PC deficiency, PS deficiency, or aPC resistance than controls. Roque and colleagues[58] showed an increased risk of preeclampsia (odds ratio 3.21, 95% confidence interval 1.20–8.58) among patients with acquired and inherited thrombophilias.

INTRAUTERINE GROWTH RESTRICTION

IUGR is a term used to describe a fetus whose estimated weight appears to be less than the 10th percentile for gestational age. IUGR is associated with an increase in fetal and neonatal mortality and morbidity rates. Although as a specialty we are becoming more proficient in diagnosing IUGR prenatally, we still do not have the ability to prevent IUGR or its recurrence. IUGR has been shown to complicate pregnancies with inherited and acquired thrombophilias.

IUGR occurs in approximately one-third of patients diagnosed with APLS[60,61] despite treatment seen in retrospective studies. This risk may be higher in untreated pregnancies. Data from Yasuda and colleagues[62] showed a significant association with IUGR observed with anticardiolipin antibodies (odds ratio 6.91, 95% confidence interval 2.70–17.68). IUGR is most often seen in the presence of severe preeclampsia, therefore it is difficult to establish causality. Some prospective studies did not see an association. A prospective cohort study of 95 nulliparous women with elevated antiphospholipid (aPL) levels at their initial prenatal visit had an increase in fetal loss but no increase in low birth weight or IUGR.[63] Pattison and colleagues[64] found no increases in IUGR, but noted increases in preeclampsia in a small cohort of 22 women.

The association between inherited thrombophilias and IUGR has not been consistently demonstrated. A recent meta-analysis examining the relationship between

IUGR and FVL, PT gene mutation, and MTHFR was performed. This analysis showed that the only association seen was with FVL and MTHFR in case-control studies. Funnel plot analysis suggested the existence of publication bias, given the small number of negative studies.[65]

There are limited studies examining AT III, PC, and PS and their association with IUGR. Roque and colleagues[58] found PC to be associated with an increased risk of IUGR (odds ratio 12.93, 95% confidence interval 2.72–61.45). Alfirevic and colleagues[54] found that women with IUGR had a higher prevalence of heterozygous G20210A PT gene mutation, homozygous MTHFR C677 T gene mutation, PS deficiency, and aPL than controls.

Placental Abruption

Some studies have shown a possible association between abruption and thrombophilias. Roque and colleagues[58] reported a significant increase in the rate of abruption with thrombophilias (odds ratio 3.60, 95% confidence interval 1.43–9.09). Robertson and colleagues[42] showed thrombophilias to be associated with an increased risk of placental abruption, but significant associations were only observed with heterozygous FVL (odds ratio 4.70, 95% confidence interval 1.13–19.59) and heterozygous PT (odds ratio 7.71, 95% confidence interval 3.01–19.76). Alfirevic and colleagues[54] found that when compared with controls, placental abruption was more often associated with homozygous and heterozygous FVL mutation, heterozygous G20210A PT gene mutation, homocysteinemia, aPC resistance, or anticardiolipin IgG antibodies. Although there appears to be an association with both inherited and acquired thrombophilia, there are no prospective trials looking at this association and how to prevent recurrence.

THROMBOPHILIA TESTING

Patients that should be tested for inherited thrombophilias are those with a personal history of VTE, a first-degree relative with a diagnosed inherited thrombophilia, or a history of IUFD when all other causes have been excluded (**Table 2**). Based on recent literature, hyperhomocysteinemia in connection with MTHFR should not be tested for. The only inherited thrombophilias that should be tested for are FVL, PT gene mutation, AT, PC, and PS. Patients that have had adverse pregnancy outcomes such as early onset preeclampsia and IUGR requiring delivery before 34 weeks, IUFD greater than 10 weeks, and recurrent pregnancy loss (>3 losses at less than 10 weeks) should undergo APLS testing. The only adverse pregnancy outcome for which an

Table 2
Recommendations for thrombophilia testing

Thrombophilia	Indications for Testing
Inherited thrombophilia	Personal history of VTE Family history of a diagnosed inherited thrombophilia[a] IUFD (when all other causes have been excluded, severe IUGR, or severe placental pathology)
Acquired thrombophilia	Personal history of VTE Recurrent pregnancy loss (>3 losses at <10 wk) IUFD (>10 wk) Severe preeclampsia (requiring delivery <34 wk) Placental insufficiency/IUGR (requiring delivery <34 wk)

[a] Need for testing is controversial.

inherited thrombophilia panel should be sent is for a fetal loss at greater than 10 weeks. The American College of Obstetrics and Gynecology (ACOG) recommends testing for inherited thrombophilias after an IUFD in cases of severe placental pathology, severe IUGR, or a family or personal history of VTE.[66] The only inherited thrombophilias that can be adequately tested for in pregnancy are FVL and PT gene mutations. FVL and PT mutations are gene mutations and are not affected by pregnancy. Testing for APLS can also be performed during pregnancy. Thrombophilia screening should be postponed during pregnancy with a new diagnosis of VTE. Thrombophilia testing should be done outside of the current thrombotic event and current anticoagulation. Diagnosis of a thrombophilia will not change management in this setting of a current VTE.

THROMBOPROPHYLAXIS

Despite the increased risk of thrombosis in pregnancy secondary to a hypercoagulable state, not every woman with a thrombophilia needs to be anticoagulated. The clinician must make sure that the benefits of anticoagulation outweigh the risks. Maternal complications with heparin and LMWH can be as high as 2%.[67–69] If the decision is made to treat, anticoagulation with heparin or LMWH should be given throughout pregnancy and up to 6 weeks postpartum. Patients can be converted to warfarin postpartum.

The clinician must first look at whether the patient has a personal history of clot and if the thrombotic event was associated with a temporary risk factor. Temporary risk factors include pregnancy, trauma, and oral contraceptive (OCP) use, surgery, immobility, and chemotherapy. Brill-Edwards and colleagues[70] prospectively studied 125 women with history of a single episode of VTE. Eighty-four of these episodes were associated with a temporary risk factor and no known thrombophilia. Anticoagulation was withheld in the antepartum period, and started for 4 to 6 weeks postpartum. Of the 84 women with an initial episode of VTE associated with a temporary risk factor, there were only 2 recurrences. Because the risk of recurrence is so low in this clinical scenario, many would consider withholding prophylactic anticoagulation until post partum in this patient population. The American College of Chest Physicians (ACCP) recommends clinical antepartum surveillance and prophylactic anticoagulation postpartum in women with a single episode of VTE associated with a temporary risk factor and without a known thrombophilia. If the temporary risk factor is pregnancy, the ACCP recommends prophylactic anticoagulation during pregnancy and post partum.[71]

Treatment of women with APLS without a thrombotic event but with an adverse pregnancy outcome remains controversial. There have only been prospective trials looking at recurrent pregnancy loss and treatment with heparin plus ASA versus ASA alone. These studies show that treatment with ASA and heparin leads to a significantly higher rate of live births in women with recurrent pregnancy loss and APLS.[51,52] Further prospective studies need to be performed looking at treatment in patients with APLS associated with history of IUFD, early-onset preeclampsia, and uteroplacental insufficiency requiring delivery before 34 weeks. Most experts and the ACOG recommend prophylactic anticoagulation and ASA during pregnancy and 6 to 8 weeks postpartum.

Treatment of women with APLS with a history of a thrombosis is much less controversial. Most experts recommend therapeutic anticoagulation plus ASA during pregnancy and 6 to 8 weeks postpartum.

Treatment of women with a known thrombophilia without a thrombotic event is also controversial. At present there is no data to support treating these patients in

pregnancy. A patient with a highly thrombogenic thrombophilia such as AT deficiency, PC, or PS may warrant therapeutic anticoagulation during pregnancy and post partum. Also patients who are homozygous for an FVL or PT gene mutation may benefit from prophylactic anticoagulation as well as compound heterozygotes for FVL and PT gene mutation; however, no data exist to support this treatment. Patients with a diagnosed inherited thrombophilia associated with IUFD may benefit from prophylactic anticoagulation.[59]

ACCP and ACOG recommend therapeutic anticoagulation in patients with history of VTE with AT III deficiency, FVL homozygous, PT gene mutation homozygous, and compound heterozygosity for FVL and PT gene mutation.[2,71] It is not clear whether patients with a history of thrombosis with PC or PS deficiency should be treated with prophylactic or therapeutic anticoagulation during pregnancy and post partum.[2]

SUMMARY

Thrombophilias have been associated with an increased risk of thrombosis and adverse pregnancy outcomes. All patients with a history of a thrombotic event should be tested for inherited and acquired thrombophilias. Given the high incidence of thrombophilia in the population and the low incidence of VTE, universal screening is not cost effective. There is some controversy regarding which patients should be screened for thrombophilias in the setting of adverse pregnancy outcomes. Women with thrombophilias appear to be at an increased risk for adverse pregnancy outcomes. With the exception of recurrent pregnancy loss in the setting of APLS, there is no clear evidence supporting that thromboprophylaxis during pregnancy improves outcome. Further randomized control trials are needed to assess the association of adverse pregnancy outcomes and whether thromboprophylaxis improves pregnancy outcome. Until it is shown that thromboprophylaxis prevents recurrent adverse pregnancy, pregnancy outcomes universal screening should not become the standard of care.

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