Management of Pregnant Women with Thrombophilia or a History of Venous Thromboembolism

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Pregnancy is associated with an increased risk of venous thromboembolism (VTE), and this condition remains an important cause of maternal morbidity and mortality. Approximately 50% of gestational VTE are associated with thrombophilia. Recent studies suggest that there is also a link between thrombophilia and pregnancy loss, as well as other gestational vascular complications. Although the most compelling data derive from women with antiphospholipid antibodies, the use of anticoagulation for prevention of these complications in women with heritable thrombophilia is becoming more frequent. This article reviews the management and prevention of VTE and other complications related to the heritable thrombophilias during pregnancy, an area that remains particularly challenging because of the potential for anticoagulant-related fetal as well as maternal complications and the paucity of good-quality data upon which to base clinical decisions.

Introduction

Pregnancy is associated with an increased risk of venous thromboembolism (VTE), and this condition remains an important cause of maternal morbidity and mortality. Recent studies suggest that there is also a link between thrombophilia and adverse pregnancy outcomes such as fetal loss as well as VTE. Although the available data are limited and flawed, the use of anticoagulation for prevention of adverse pregnancy outcomes in women with heritable thrombophilias is increasing. The use of anticoagulant therapy during pregnancy is challenging because of the potential for fetal as well as maternal complications. Although evidence-based recommendations for the use of anticoagulants in pregnancy have been published,[1] given the paucity of available data, these guidelines are based largely upon extrapolations from data in nonpregnant patients in addition to case reports and case series of pregnant patients.

Anticoagulant Use during Pregnancy

When selecting optimal therapy for VTE during pregnancy, the risks posed by any drug to the fetus must be considered, in addition to the regimen's efficacy and maternal safety. Potential fetal complications of maternal anticoagulant therapy include teratogenicity, bleeding, and loss. Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and danaparoid cannot cross the placenta[2-4] and, therefore, are safe anticoagulant choices for the fetus.[5-7] Vitamin K antagonists cross the placenta and have the potential to cause all these complications (**Table 1**).[8] The nasal hypoplasia and stippled epiphyses of coumarin embryopathy can occur if vitamin K antagonists are taken between weeks 6 and 12 of gestation,[8,9] while central nervous system abnormalities can occur with exposure in any trimester.[9] Investigations have documented placental transfer of r-hirudin in rabbits and rats.[7] Small numbers of case reports of successful outcomes with r-hirudin use in pregnancy have been published;[7] however, there are insufficient data to evaluate its safety in this setting. Although no placental passage of fondaparinux was demonstrated in an *in vitro* human cotyledon model,[10] anti–factor Xa activity (at approximately one-tenth the concentration of maternal plasma) was found in the umbilical cord plasma in newborns of 5 mothers treated with fondaparinux.[11] Although there have been reports of the successful use of this agent in pregnant women,[12] potential deleterious effects of fondaparinux on the fetus cannot be excluded. Thus, clinicians should reserve the use of direct thrombin inhibitors and fondaparinux for those pregnant women with heparin-induced thrombocytopenia (HIT) or a history of HIT who cannot receive danaparoid (at the time of writing, danaparoid is not available in the U.S.).

Maternal complications of anticoagulant therapy are similar to those seen in nonpregnant patients and include bleeding (for all anticoagulants), as well as HIT, heparin-associated osteoporosis, and pain at injection sites for heparin-related compounds.[13] Despite a paucity of supportive data from controlled trials or even large prospective observational studies, LMWH is now commonly used for prophylaxis and treatment of maternal VTE. LMWH is preferred to UFH for most patients because of its better bioavailability, longer plasma-half-life, more predictable dose response, and improved safety profile with respect to heparin-associated osteoporosis and HIT (**Table 2**).[13,14] Furthermore, large trials in nonpregnant patients have demonstrated that LMWH is at least as safe and effective as UFH for the initial treatment of VTE[15,16] as well as for prophylaxis in high-risk patients.[14] Additional studies in the nonpregnant population have also demonstrated that long-term

Table 1. Fetal complications reported with maternal vitamin K antagonist use during pregnancy.*

Anticoagulant regimen	Spontaneous abortions	Congenital anomalies	Fetal wastage
Vitamin K antagonists throughout with/without heparin near term	196/792 (24.8%)	35/549 (6.4%)	266/792 (33.6%)
Heparin starting at/before 6 weeks and throughout 1st trimester, then vitamin K antagonists with/without heparin near term	19/129 (14.7%)	0/108 (0.0%)	21/129 (16.3%)
No anticoagulation	2/35 (5.7%)	2/33 (6.1%)	7/35 (20.0%)

*Pregnant women with mechanical heart valves
Data are from Chan et al.[8]

LMWH and UFH are as effective and safe as vitamin K antagonists for the prevention of recurrent VTE.[17,18]

Venous Thromboembolism during Pregnancy

Pulmonary embolism (PE) remains the major cause of maternal mortality in the western world,[19] and VTE in pregnancy is an important cause of maternal morbidity.[20] Results from studies in which either all or most patients underwent accurate diagnostic testing for VTE report that the incidence of VTE ranges from 0.6 to 1.3 episodes per 1000 deliveries.[21] Although these rates are low, they represent a 5- to 10-fold increase in risk compared with those reported for nonpregnant women of comparable age. A meta-analysis showed that two-thirds of deep vein thrombosis (DVT) occur antepartum, with these events distributed relatively equally throughout all three trimesters.[22] In contrast, 43% to 60% of pregnancy-related episodes of PE appear to occur in the 4 to 6 weeks after delivery.[23,24] Since the antepartum period is substantially longer than the 6-week postpartum period, the daily risk of DVT, as well as PE, is considerably higher following delivery than antepartum.

Recommended approach to treatment of VTE during pregnancy

Regimens for the initial treatment of VTE are outlined in **Table 3**. If LMWH is used, a weight-adjusted dose regimen should be used. LMWH requirements may alter as pregnancy progresses because the volume of distribution of LMWH changes and glomerular filtration rate increases in the second trimester. The need for dose adjustments over the course of pregnancy remains controversial. Some suggest that the dose should be increased in proportion to the change in weight.[25] On the basis of small studies showing the need for dose-escalation to maintain "therapeutic" anti-Xa LMWH levels,[26] some advocate the performance of periodic (e.g., every 1 to 3 months) anti–factor Xa LMWH levels 4 to 6 hours after injection, with dose-adjustment to maintain a "therapeutic" anti-Xa level (0.6 to 1.0 U/mL if a twice-daily regimen is used; slightly higher if a once-daily regimen is chosen). However, other researchers have demonstrated that few women require dose adjustment when therapeutic doses of LMWH are used.[27] In the absence of large studies using clinical endpoints demonstrating that there is an optimal "therapeutic anti-Xa LMWH range" or that dose adjustments increase the safety or efficacy of therapy, any of these approaches is reasonable. Clinicians selecting UFH can use either initial intravenous therapy followed by subcutaneous UFH given every 12 hours in doses adjusted to maintain a therapeutic activated partial thromboplastin time (aPTT) 6 hours after injection or twice-daily adjusted-dose subcutaneous UFH for both initial and

Table 2. Safety of low molecular weight heparin (LMWH) use during pregnancy.*

Complication	Frequency, % (95% CI)
Antenatal bleeding	0.43 (0.22-0.75)
Allergic skin reaction	1.80 (1.34-2.37)
Osteoporotic fracture	0.04 (<0.01-0.20)
Thrombcytopenia (platelets <100 x 10^9/L)	0.11 (0.02-0.32)
Confirmed HIT	0.00 (0.00-0.11)

Data are from Greer and Nelson-Piercy.[13]
*For all indications and all LMWH; *N* = 2777

Table 3. Initial treatment for venous thromboembolism during pregnancy.

Anticoagulant	Regimen
Low-molecular weight heparin	Weight based doses given subcutaneously once or twice daily. · Dalteparin: 100 U/kg twice daily or 200 U/kg daily · Enoxaparin: 1 mg/kg twice daily or 1.5 mg/kg once daily · Tinzaparin: 175 U/kg once daily
Unfractionated heparin	Continuous infusion of intravenous heparin adjusted to maintain a therapeutic aPTT or subcutaneous heparin every 12 hours in doses adjusted to prolong the aPTT 6 hours after injection into the therapeutic range.

Abbreviations: aPPT, activated partial thromboplastin time

long-term treatment.

It remains unclear whether the dose of UFH or LMWH can be reduced after an initial phase of therapeutic anticoagulation. It has been suggested that full-dose anticoagulation should be maintained throughout pregnancy and the puerperium because of the ongoing risk of recurrent VTE during this time period. However, regimens in which the intensity of LMWH is reduced later during the course of therapy to an intermediate dose regimen[28] or 75% of a full treatment dose[18] have been used successfully in the nonpregnant population. Although there have been no studies directly examining this strategy in pregnant women, a modified dosing regimen may be useful in those at increased risk of anticoagulant-related bleeding or heparin-induced osteoporosis.

Management of anticoagulant therapy at the time of delivery

In order to avoid an unwanted anticoagulant effect during delivery (especially with neuroaxial anesthesia) in women receiving adjusted-dose subcutaneous UFH[29] or LMWH, UFH or LMWH can be discontinued 24 to 36 hours before elective induction of labor or cesarean section.[30] If spontaneous labor occurs in fully anticoagulated women, neuroaxial anesthesia should not be used. In women receiving subcutaneous UFH, careful monitoring of the aPTT is required and, if it is markedly prolonged, protamine sulfate may be required to reduce the risk of bleeding. If available, anti-Xa LMWH levels should be checked in women treated with LMWH. If bleeding occurs, protamine sulfate may provide partial neutralization.[31] There are reports of the successful use of recombinant activated factor VII concentrate to reverse LMWH-induced bleeding in nonpregnant patients with underlying hypercoagulable states;[32] however, experience with this strategy is limited, and there continue to be concerns about the thrombogenicity of recombinant factor VIIa. Therefore, this intervention should be reserved for major bleeding unresponsive to conventional therapy.[33]

Women with a very high risk for recurrent VTE (e.g., proximal DVT or PE within 4 weeks prior to the expected date of delivery) can be switched to therapeutic intravenous UFH upon admission to hospital for induction. The UFH infusion is then discontinued 4 to 6 hours prior to the expected time of epidural insertion or delivery. With this approach, the duration of time without therapeutic anticoagulation can be shortened considerably. Alternatively, others in this situation have used retrievable inferior vena caval filters that can be removed postpartum.[34]

Postpartum LMWH or UFH therapy should be recommenced as soon as it is safe to do so, usually within 12 to 24 hours of delivery. Prophylactic doses of these agents should not be given sooner than 2 hours after epidural catheter removal (with a longer delay for bloody or traumatic neuroaxial procedures).[35] Although there are no definite recommendations for the timing of resumption of full-dose LMWH or UFH following epidural catheter removal, it appears safe to do so within 24 hours of catheter removal (unless catheter placement was bloody or traumatic, in which case the initiation of full-dose therapy should be delayed for at least 48 hours).

Postpartum warfarin can be started at the same time as LMWH or UFH therapy is initiated. Heparin is continued until an international normalized ratio (INR) of 2.0 or greater is reached. There are no appropriately designed trials to guide the duration of postpartum anticoagulation for women diagnosed with VTE during pregnancy. In general, it is recommended that treatment should continue for a minimum of 6 months and until at least 6 weeks postpartum.

Prevention of VTE in Pregnant Women

Women with thrombophilia and those with a history of VTE are also believed to have a increased risk of DVT or PE in subsequent pregnancies.[36,37] Thromboprophylaxis during pregnancy is problematic because it involves long-term parenteral UFH or LMWH. Both are expensive, inconvenient and painful to administer, and associated with risks for bleeding, osteoporosis, and HIT, although these complications, particularly HIT, are very uncommon with LMWH (**Table 2**).[13] Rational administration of prophylaxis depends on accurately quantifying the risk of thrombosis and identifying those women whose risk is sufficiently high to merit intervention. The threshold for recommending postpartum prophylaxis is lower than for antepartum prophylaxis due to the shorter length of required treatment (i.e., 6 weeks), the higher average daily risk of VTE in the postpartum period,[22-24] and the fact that warfarin can be used safely during this time even in women who are breastfeeding, since it does not appear in the breast milk.[38,39]

Pregnant women with thrombophilia and no prior VTE

Approximately 50% of gestational VTE are associated with heritable thrombophilia.[40] A number of studies have examined the relationship between hereditary thrombophilias and pregnancy-related VTE. However, methodologic limitations have made it difficult to obtain an accurate assessment of these risks. In a recent systematic review of 9 studies that assessed the risk of VTE in pregnant women with heritable thrombophilias, all congenital thrombophilias with the exception of homozygosity for the thermolabile methylene tetrahydrofolate reductase variant (MTHFR C677T) were found to be associated with a statistically significant increase in the risk of pregnancy-related VTE (**Table 4**).[36] Given a background incidence of VTE during pregnancy of approximately 1 in 1000 deliveries, it is clear that the absolute risk of VTE in women without a prior event remains modest for those who have the most common inherited thrombophilias (heterozygosity for factor V Leiden or prothrombin G20210A variant). Consistent with this, Dizon-Townson and colleagues reported no episodes of VTE among members of a prospectively followed cohort of 134 factor V Leiden mutation carriers with a single-

Table 4. Risk of pregnancy-associated venous thromboembolism(VTE) in thrombophilic women without prior disease.

Thrombophilia	Relative Risk of VTE OR (95% CI)	Estimated absolute risk of VTE events per 1000 patients*
Factor V Leiden (heterozygous)	8.32 (5.44-12.70)	8/1000
Prothrombin gene variant (heterozygous)	6.80 (2.46-18.77)	6/1000
Factor V Leiden (homozygous)	34.40 (9.86-120.05)	34/1000
Prothrombin gene variant (homozygous)	26.36 (1.24-559.20)	26/1000
Antithrombin deficiency	4.69 (1.30-16.96)	4/1000
Protein C deficiency	4.76 (2.15-10.57)	4/1000
Protein S deficiency	3.19 (1.48-6.88)	3/1000
MTHFR C677T (homozygous)	0.74 (0.22-2.48)	1/1000

*Assuming a baseline risk of 1 event per 1000 pregnant patients without a known thrombophilia
Data are from Robertson et al.[36]
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; MTHFR, methylene tetrahydrate folate reductase

ton pregnancy and no prior history of VTE (0%; 95% CI, 0-2.7%).[41] In other cohort studies, the absolute risk of pregnancy-associated VTE has been reported to range from 9% to 16% in homozygotes for the factor V Leiden mutation, while the risk for those with those double heterozygosity for factor V Leiden and prothrombin G20210A variant has been reported as 4.0% (95% CI, 1.4-16.9%).[42]

The risk of pregnancy-related VTE in the systematic review described above is lower for women with deficiencies of the natural anticoagulants than traditionally reported.[36] This is likely due to differences in patient population and criteria used to define the presence of a thrombophilia.[36] Conflicting results have been reported in other recent studies. In a retrospective study of 72,000 pregnancies in which women with venous thrombosis were assessed for thrombophilia and the underlying prevalence of these defects in the population was known, the risk of VTE was 1:437 for women with the factor V Leiden mutation, 1:113 for those with protein C deficiency, 1:2.8 for women with type 1 antithrombin deficiency and 1:42 for those with type 2 antithrombin deficiency.[43] Gerhardt and colleagues reported similar findings when they used the results of their case control study and an assumed underlying gestational VTE rate of 0.66 per 1000 pregnancies to calculate positive predictive values of 1:500 for individuals heterozygous for the factor V Leiden mutation, 1:200 for those heterozygous for the prothrombin G20210A variant, and 4.6:100 for double heterozygotes.[44] These data suggest that women with antithrombin deficiency or homozygosity for the factor V Leiden mutation, as well as double heterozygotes, may need to be managed more aggressively than those with other heritable thrombophilias.

The majority of studies that have examined the risk of VTE in pregnancy have focused on these heritable thrombophilic mutations; as a result, the risk of pregnancy-related VTE with acquired thrombophilic abnormalities remains unclear. Persistent antiphospholipid antibodies (lupus anticoagulants [nonspecific inhibitors] or anticardiolipin antibodies) are likely associated with an increased risk of pregnancy-related VTE.

Given our limited knowledge of the natural histories of the various thrombophilias, the low predicted absolute rates of thrombosis in those with the most common thrombophilias, and a lack of trials of VTE prophylaxis in this population, the management of pregnant women with known thrombophilia and no prior VTE remains controversial. Postpartum prophylaxis for approximately 6 weeks using either warfarin targeted to an INR of 2.0 to 3.0 with a short initial course of UFH or LMWH or prophylactic doses of LMWH is generally recommended for all women with a confirmed hypercoaguable state, even in the absence of prior VTE. Antepartum, both careful clinical surveillance and pharmacologic prophylaxis are acceptable management options. The indication for active antepartum prophylaxis appears stronger for women with antithrombin deficiency, homozoygosity for the factor V Leiden or prothrombin gene variant, persistent positivity for antiphospholipid antibodies, or combined thrombophilias.

Commonly used prophylactic regimens are outlined in **Table 5**. Until comparative studies are performed, it is not possible to make definitive recommendations about which prophylactic regimen should be used (if active prophylaxis is chosen). Given its benefits compared with UFH, LMWH is generally the preferred agent for prophylaxis. The need to adjust prophylactic LMWH dosing according to anti-Xa levels remains controversial. The increased renal clearance of LMWH during pregnancy has led some to suggest that clinicians undertake periodic monitoring of the anticoagulant effect because anticoagulant activity may decrease as pregnancy progresses. On the other hand, the appropriate "therapeutic range" for prophylaxis is uncertain, and it has not been shown that dose adjustment to attain a specific anti-Xa level increases safety or efficacy of prophylaxis.

Prior VTE and pregnancy

The extent to which pregnancy influences the risk of recurrent VTE remains somewhat uncertain. In a retrospective study of 109 women who had at least one pregnancy without receiving thrombosis prophylaxis after an episode of VTE, recurrence rates per 100 patient-years were 10.9%

Table 5. Dosing regimens for venous thromboembolism prophylaxis.*

Regimen	Dose
Prophylactic UFH	UFH 5000 U subcutaneously every 12 hours
Intermediate-dose UFH	UFH subcutaneously every 12 hours in doses adjusted to target an anti-Xa level of 0.1-0.3 U/mL
Prophylactic LMWH	Enoxaparin 40 mg subcutaneously every 24 hours Dalteparin 5000 units subcutaneously every 24 hours Tinzaparin 4500 units or 75 units/kg subcutaneously every 24 hours
Intermediate-dose prophylactic LMWH	Dalteparin 5000 U subcutaneously every 12 hours Enoxaparin 40 mg subcutaneously every 12 hours LMWH subcutaneously every 24 hours adjusted to achieve a peak anti-Xa level of 0.2-0.6 U/mL

*These dosing regimens are not FDA approved for this indication.
Abbreviations: UFH, unfractionated heparin; LWMH, low-molecular-weight heparin

during and 3.7% outside of pregnancy (relative risk [RR] during pregnancy, 3.5; 95% CI, 1.6-7.8).[37] In order to obtain a reliable estimate of the true incidence of recurrence in women with prior VTE, Brill-Edwards and colleagues performed a prospective study of 125 pregnant women with a single previous episode of objectively diagnosed VTE.[45] Women with an episode of VTE within 3 months before pregnancy or a prior documented hypercoagulable state were excluded from study participation. Ninety-five patients underwent blood testing to identify laboratory abnormalities. Antepartum heparin was withheld and anticoagulants (usually warfarin with a target INR of 2.0 to 3.0 with an initial short course of UFH or LMWH) were given in the postpartum period for 4 to 6 weeks. The risk of antepartum recurrent VTE was 2.4% (95% CI, 0.2-6.9%). The effect of thrombophilia and the circumstances surrounding the prior episode of VTE was explored in a *post-hoc* subgroup analysis. There were no recurrences among the 44 women without thrombophilia and a previous episode of thrombosis associated with a temporary risk factor (0%; 95% CI, 0.0-8.0%). However, the risk of recurrence appeared higher in pregnant women with thrombophilia and/or a prior episode of unprovoked VTE (5.9%; 95% CI, 1.2-16.0%).

Some have suggested that the advanced median gestational age at enrollment (approximately 15 weeks) and the exclusion of women with known thrombophilia in the Brill-Edwards study might result in an underestimate of the true risk of pregnancy-related recurrent VTE. In a subsequently published retrospective cohort study of 159 women with at least one pregnancy after VTE, the probability of antepartum VTE in those not given antepartum prophylaxis was 6.2% (95% CI, 1.6-10.9%), while that for postpartum VTE was 6.5% (95% CI, 3.5-11.9%).[46] In this study, the presence or absence of temporary risk factors or of a definable thrombophilia did not appear to influence the risk of recurrent VTE associated with pregnancy. The retrospective nature of this study, differences in study population (including the inclusion of women with more than one prior episode of VTE), and failure to independently adjudicate recurrent events might account for the higher risk of recurrence in this study. However, in both studies, the overall risk of antepartum recurrent VTE was less than 10%, and CIs around the risk estimates are overlapping.

Thus, although available data suggest that women with prior VTE have an increased risk of recurrence during pregnancy, the absolute recurrence rates, both overall and in patient subgroups, are unknown. There have been no large clinical trials assessing the role of prophylaxis in pregnant women with previous VTE. As a result, recommendations for antepartum prophylaxis are primarily based on the risk estimates reported by Brill-Edwards and colleagues.[45] However, all decisions should be considered on an individual basis, taking all the woman's risk factors for VTE, along with patient preference, into consideration. Antepartum prophylaxis generally appears unwarranted in women without thrombophilia whose previous episode of thrombosis was associated with a temporary risk factor. Although pregnancy and oral contraceptive therapy were included as transient risk factors in the Brill-Edwards study, the number of women whose prior event occurred in the setting of increased estrogen was small, and many experts believe that these women have sufficiently high risk of antepartum recurrence to merit prophylaxis prior to delivery as well as postpartum. At present, either clinical surveillance or prophylaxis antepartum can be defended in pregnant women with prior unprovoked VTE or VTE associated with a thrombophilia. Antepartum prophylaxis is easier to justify in women with higher-risk thrombophilias, as outlined in the previous section, and in those with more than one prior event. **Table 5** lists common prophylactic regimens. Although supportive data from clinical trials are lacking, postpartum prophylaxis with either warfarin targeted to an INR of 2.0 to 3.0 or prophylactic LMWH is suggested for pregnant women with prior VTE.

Hereditary Thrombophilia and Pregnancy Complications

Adverse pregnancy outcomes are not infrequent; 25% of human conceptions end in miscarriage. Of those, 5% of women experience 2 or more successive losses and 1% to 2% have 3 or more consecutive losses.[47] Maternal or fetal anatomic, chromosomal, endocrinologic or immunologic problems are detected in a small number of cases of recurrent loss but for most a cause is not identified. Pre-eclampsia, a leading cause of both fetal and maternal morbidity and mortality, is seen in 3% to 7% of pregnancies, while placental abruption is uncommon (0.5% of gestations) but carries a high risk of fetal mortality.[48]

The most compelling data for a link between thrombo-

philia and pregnancy complications derives from studies in women with antiphospholipid antibodies. There is substantial interest in examining whether heritable thrombophilias are also associated with adverse pregnancy outcomes, and whether this can be ameliorated by antithrombotic therapy. Many studies have examined the association between thrombophilia and pregnancy complications, often with differing results,[36,49] likely reflecting heterogeneity of study design, sample size, inclusion criteria, population studied, outcome definition, and thrombophilias studied. However, the results of a recent systematic review that examined 25 studies in 7167 women confirm associations with some hereditary thrombophilias and early (recurrent) fetal loss, late fetal loss, pre-eclampsia, and placental abruption (**Table 6**).[36] The association between intrauterine growth restriction (IUGR) and thrombophilia remains controversial. In this systematic review, there was a trend towards an increased risk of IUGR in women with congenital thrombophilia, but no statistically significant associations were found.[36]

Given the uncertainty associated with the magnitude of risk, the uncertainty associated with any benefits of prophylaxis in women with thrombophilia (outlined below), and the uncertainty about the effect on anxiety and well-being in women screened versus not screened, whether screening is in the best interests of women with early pregnancy loss remains uncertain.

In view of the data showing an association between hereditary thrombophilia and adverse pregnancy outcomes, clinicians are increasingly using antithrombotic therapy in women at risk of these complications. However, the data surrounding the use of antithrombotic therapy in women with hereditable thrombophilia and pregnancy loss are less convincing than those in women with antiphospholipid antibodies, and consist predominantly of small uncontrolled trials or observational studies. Prospective cohort studies of pregnant women with hereditary thrombophilia with recurrent pregnancy losses have reported an increase in the frequency of live births with LMWH compared with a previous untreated pregnancy[50] or concurrent untreated patients.[51] In the LIVE-ENOX trial, in which women with hereditary thrombophilia and recurrent pregnancy loss were randomized to one of two doses of enoxaparin (40 mg/day and 80 mg/day), there was no significant difference in pregnancy outcomes between the two groups; however, the rate of live births was higher than might have been expected given the patients' prior histories.[52] There has been considerable debate about this trial focusing on its limitations, particularly the absence of an untreated control group, the heterogeneous entry criteria, and the risk of regression toward the mean with the use of a historic comparison group. Recently, Gris and colleagues reported that treatment with 40 mg enoxaparin daily in pregnant women with a thrombophilia (factor V Leiden, prothrombin gene mutation, or protein S deficiency) and one previous pregnancy loss after 10 weeks gestation, resulted in a significantly higher live birth rate (86%) compared with low-dose aspirin alone (29%).[53] However, this trial also has significant limitations, including small sample size, absence of an untreated control group, and inadequate concealment of allocation. Further, given the relatively high success rate of subsequent pregnancies after a single miscarriage, it is difficult to assess the implications of these results.

The data described above provide some circumstantial evidence that LMWH may improve the pregnancy outcome in women with heritable thrombophilia and recurrent pregnancy loss or loss after 10 weeks; however, available studies have important methodologic limitations, and

Table 6. Risk of pregnancy complications in women with inherited thrombophilias.

Thrombophilia	Early (recurrent) loss, OR (95% CI)	Late loss, OR (95% CI)	Pre-eclampsia, OR (95% CI)	Placental abruption, OR (95% CI)	IUGR, OR (95% CI)
Factor V Leiden (homozygous)	2.71 (1.32-5.58)	1.98 (0.40-9.69)	1.87 (0.44-7.88)	8.43 (0.41-171.20)	4.64 (0.19-115.68)
Factor V Leiden (heterozygous)	1.68 (1.09-2.58)	2.06 (1.10-3.86)	2.19 (1.46-3.27)	4.70 (1.13-19.59)	2.68 (0.59-12.13)
Prothrombin gene variant (heterozygous)	2.49 (1.24-5.00)	2.66 (1.28-5.53)	2.54 (1.52-4.23)	7.71 (3.01-19.76)	2.92 (0.62-13.70)
MTHFR C677T (homozygous)	1.40 (0.77-2.55)	1.31 (0.89-1.91)	1.37 (1.07-1.76)	1.47 (0.40-5.35)	1.24 (0.84-1.82)
Antithrombin deficiency	0.88 (0.17-4.48)	7.63 (0.30-196.36)	3.89 (0.16-97.19)	1.08 (0.06-18.12)	NA
Protein C deficiency	2.29 (0.20-26.43)	3.05 (0.24-38.51)	5.15 (0.26-102.22)	5.93 (0.23-151.58)	NA
Protein S deficiency	3.55 (0.35-35.72)	20.09 (3.70-109.15)	2.83 (0.76-10.57)	2.11 (0.47-9.34)	NA

Data from Robertson et al.[36]
Abbreviations: IUGR, intrauterine growth restriction; OR, odds ratio; CI, confidence interval

firm recommendations cannot be made regarding the use of antithrombotic therapy in this patient population. Decisions should be made after reviewing with the patient the limitations of the available data, along with the potential benefits, harms, and costs of any intervention. It is important to note that treatment that prevents fetal loss may not prevent other complications and, at present, there are insufficient data on the effect of antithrombotic interventions in other adverse pregnant outcomes in women with hereditary thrombophilia to provide any recommendations.

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