Thromboprophylaxis in Pregnancy: Who and How?

Sarah M. Davis, MD, D. Ware Branch, MD*

Venous thrombosis and embolism (VTE) is one of the most common, serious complications associated with pregnancy, and now ranks as a leading cause of maternal morbidity and mortality in developed countries.1 Information regarding the association of VTE with acquired and heritable thrombophilias has greatly expanded in the last 20 years, adding a new layer of complexity to decisions about thromboprophylaxis. The objective of this review is to detail which patients are at clinically important increased risk for VTE, are candidates for thrombophilia screening, and warrant thromboprophylaxis. Suggested management schemes for use in specific patient subgroups are also provided.

EPIDEMIOLOGY

Pregnancy and the postpartum period carry an increased risk of VTE, with an incidence between 0.61 and 1.72 per 1000 deliveries.2,3 Compared with nonpregnant women, pregnant and postpartum women are approximately 4 to 5 times more likely to develop VTE.4 Roughly equal proportions of clinically apparent, pregnancy-related venous thromboembolic events are diagnosed in the antepartum and postpartum periods.3 The risk of antepartum VTE was highest in the third trimester in one study.5 In contrast, others found an increased risk in early pregnancy.6,7 Overall, in these studies the risk of antepartum VTEs were evenly distributed throughout each trimester.6,7

In general, deep venous thrombosis (DVT) is more commonly diagnosed than pulmonary embolism (PE) in pregnancy. When DVT presents during pregnancy, it is more likely to be in the left lower extremity.2,8 Predominance of left lower extremity clot formation may be due to compression of the left common iliac vein by the enlarging gravid uterus.9 Pelvic venous thrombosis is a rare manifestation of deep venous thrombosis in nonpregnant individuals, and has been cited in a large prospective registry of DVT in the United States as accounting for less than 1% of DVTs.10 Obstetricians should be
aware that pelvic venous thrombosis is more common in pregnancy, occurring in approximately 11% to 13% of venous thrombotic cases.\(^7,11\)

Of importance is that PE is more likely to be diagnosed in the postpartum period.\(^2–4\) This, coupled with the relatively higher incidence of VTE in the postpartum period, is cause for appropriate deliberation regarding postpartum thromboprophylaxis in at-risk patients.

**PATHOPHYSIOLOGY AND RISK FACTORS**

Virchow’s triad describes 3 elements that contribute to the development of thrombosis: (1) stasis, (2) vascular trauma, and (3) hypercoagulability. These elements are all present during pregnancy and the postpartum period. Lower extremity venous stasis has been demonstrated during pregnancy.\(^12\) Venous flow velocity decreases with advancing gestation, and is lower in the left compared with the right lower extremity. In addition, venous distention has been demonstrated, which may result in endothelial damage and prothrombotic changes in the endothelium.\(^13\) Macklon and Greer\(^14\) found that lower extremity venous flow velocity increased and vessel diameter decreased between 4 and 42 days postpartum. Venous flow velocity and diameter returned to levels observed in early pregnancy at the 42-day measurement.\(^13,14\) In addition to mechanical compression of pelvic veins, increased circulating levels of estrogen and local production of prostacyclin and nitric oxide increase deep venous capacitance during pregnancy.\(^15\)

Vascular trauma in the form of endothelial damage may occur due to venous distention during pregnancy,\(^13\) or may occur during conditions such as preeclampsia where vascular endothelial activation is present.\(^16\) During normal delivery, venous compression may occur. Operative and assisted deliveries are thought to contribute to vascular trauma, also possibly contributing to the risk of thrombosis in the postpartum period; this is especially true for cesarean delivery.

Normal pregnancy is accompanied by changes in the hemostatic system that would seem to result in a hypercoagulable state for the prevention of hemorrhage at the time of delivery. Overall, most clotting factors increase, some anticoaguclants decrease, and fibrinolytic activity decreases. Regarding specific factors, factors II, VII, VIII, IX, XII, and von Willebrand factor increase throughout pregnancy.\(^17\) Fibrinogen levels increase to levels that are almost twice that of the nonpregnant state.\(^17,18\) Anticoagulant changes include decreased free and total protein S antigen levels, as well as decreased activity, occurring very early in pregnancy. Although protein C levels remain unchanged,\(^17,19\) an overall increase in activated protein C resistance is present, with the degree of resistance dependent on several modifiers, including the presence of the Factor V Leiden mutation (FVLM), thrombin generation, and the presence of antiphospholipid antibodies.\(^20\) Fibrinolysis is decreased, predominantly due to diminished tissue plasminogen activator activity. Increases have been noted in plasminogen activator inhibitor-1 and -2, and thrombin activatable fibrinolysis inhibitor. Other markers of a hypercoagulable state include increased thrombin-antithrombin complexes, prothrombin fragments 1 and 2, peak thrombin generation, and increased D-dimer levels.\(^17–19\)

**CLINICAL RISK FACTORS**

Specific clinical risk factors have been identified that impact the likelihood of VTE. Not surprisingly, these are typically related to the elements of Virchow’s triad and include such factors as bed rest (ie, stasis), operative delivery (ie, vascular trauma), and heritable thrombophilias (ie, hypercoagulability). Maternal age 35 years or older and
cesarean delivery confer significant risk. Complications of pregnancy and delivery that increase the odds of VTE include critical illness, transfusion, and postpartum infection.\textsuperscript{3} \textbf{Table 1}, modified from the work of James and colleagues,\textsuperscript{3} shows the odds ratios associated with pertinent risk factors regarding risk of VTE.

Also shown in \textbf{Table 1} are the odds ratios associated with several common antenatal and postnatal risk factors both alone and in combination; these are modified from the work of Jacobsen and colleagues.\textsuperscript{21} For example, the risk of VTE is substantially increased with the combination of antepartum bed rest and an increased body mass index (weight in kilograms divided by height in meters squared), or with postpartum infection following cesarean delivery.\textsuperscript{21}

\textbf{ACQUIRED AND HERITABLE THROMBOPHILIAS}

The overall VTE risk associated with specific thrombophilias is well described in a systematic literature review by Robertson and colleagues in 2005.\textsuperscript{22} Odds ratios were increased to varying degrees for FVLM (homozygous and heterozygous),

\begin{table}[h]
\centering
\begin{tabular}{|l|c|}
\hline
\textbf{Condition} & \textbf{Odds Ratio (95\% Confidence Interval)} \\
\hline
\textbf{Medical Complications} & \\
Hypertension & 1.8 (1.4–2.3) \\
Heart disease & 7.1 (6.2–8.3) \\
Thrombophilia & 51.8 (38.7–69.2) \\
History of thrombosis & 24.8 (17.1–36.0) \\
Antiphospholipid syndrome & 15.8 (10.9–22.8) \\
Sickle cell disease & 6.7 (4.4–10.1) \\
Lupus & 8.7 (5.8–13.0) \\
Diabetes & 2.0 (1.4–2.1) \\
Obesity & 4.4 (3.4–5.7) \\
\hline
\textbf{Antepartum risk} & \\
Body mass index (BMI) >25 & 1.8 (1.3–2.4) \\
Antepartum immobilization & 7.7 (3.2–19.0) \\
BMI >25 and antepartum immobilization & 62.3 (11.5–337.6) \\
Smoking (10–30 cigarettes/d) & 2.1 (1.3–3.4) \\
Spontaneous twin gestation & 2.6 (1.1–6.2) \\
ART twin gestation & 6.6 (2.1–21.0) \\
\hline
\textbf{Postpartum risk} & \\
Smoking (10–30 cigarettes/d) & 3.4 (2.0–5.5) \\
Hemorrhage (without surgery) & 4.1 (2.3–7.3) \\
Hemorrhage (with surgery) & 12.0 (3.9–36.9) \\
Infection (vaginal delivery) & 20.2 (6.4–63.5) \\
Infection (cesarean delivery) & 6.2 (2.4–16.2) \\
Planned cesarean & 1.3 (0.7–2.2) \\
Acute cesarean & 2.7 (1.8–4.1) \\
\hline
\end{tabular}
\caption{Clinical risk factors for venous thrombosis or embolism}
\end{table}

prothrombin gene mutation (PGM) (homozygous and heterozygous), antithrombin deficiency, protein C and protein S deficiency, and antiphospholipid antibodies (Table 2). Of note, the C677T methylene tetrahydrofolate reductase mutation was not significantly associated with VTE.

The 2 most common heritable thrombophilias, heterozygosity for FVLM and PGM, have been examined in prospective observational studies and have not been found to pose a clinically important risk of VTE in otherwise healthy pregnant women with no history of thrombosis.29–25 Deficiency of antithrombin, protein C, or protein S and antiphospholipid antibodies have not been studied in the same way, largely due to their infrequency.

THE ROLE OF THROMBOPHILIA TESTING

While the association between thrombophilias and VTE is apparent, the utility and cost-effectiveness of screening pregnant women for these disorders is not. Most experts agree that universal screening of asymptomatic women is not cost effective.26–28 Obstetricians are left with the question of who should be screened. When considering thrombophilia screening, it may be helpful to think of candidate patients as falling into 1 of 4 categories: (1) those with acute VTE, (2) those with recurrent VTE (2 or more events), (3) those with a personal history of a single, prior VTE, or (4) those with a family history of VTE but without a personal history of VTE.

Acute VTE is not the subject of this review, but clinicians should recognize that testing for heritable thrombophilias in the setting of a first episode of VTE is controversial,29 largely because the findings are not likely to change management and certainly will not alter the usual acute management with heparin and transition to warfarin (in nonpregnant patients). In addition, the heritable thrombophilias most commonly found, heterozygosity for FVLM or PGM, are not indications for long-term anticoagulation. Testing for antiphospholipid syndrome (via lupus anticoagulant, anticardiolipin, and anti–β2-glycoprotein I) is common practice in a first-episode VTE because patients with antiphospholipid syndrome should be considered for long-term anticoagulation.30

Most women with recurrent VTE will have been screened for thrombophilias, and hence will not require consideration of screening. Regardless, the risk in women with recurrent VTE is generally sufficient to warrant long-term anticoagulation. Such

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Thrombophilia risk factors for venous thrombosis or embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophilia22</td>
<td>Odds Ratio (95% Confidence Interval)</td>
</tr>
<tr>
<td>Factor V Leiden homozygous</td>
<td>34.40 (9.86–120.05)</td>
</tr>
<tr>
<td>Factor V Leiden heterozygous</td>
<td>8.32 (5.44–12.70)</td>
</tr>
<tr>
<td>Prothrombin G20210A homozygous</td>
<td>26.36 (1.24–559.29)</td>
</tr>
<tr>
<td>Prothrombin G20210A heterozygous</td>
<td>6.80 (2.46–18.77)</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>4.69 (1.30–16.96)</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>4.76 (2.15–10.57)</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>3.19 (1.48–6.88)</td>
</tr>
</tbody>
</table>

patients are typically candidates for full anticoagulation, rather than thromboprophylaxis, during pregnancy.

Many women with a personal history of a single, prior VTE and who are not on long-term anticoagulants will have been tested for heritable and acquired thrombophilias by physicians other than their obstetricians. When considering pregnancy, those women with a single prior VTE episode previously tested for and known to be positive for a thrombophilia should be managed according to guidelines outlined later in this discussion. However, for many clinicians it is the patients who have not been previously tested for thrombophilias that are most confusing, especially because the current American College of Obstetrician and Gynecologists (ACOG) practice guidelines suggest that these women should be “offered testing, especially if such testing would affect management.”

One way in which thrombophilia testing might alter pregnancy management is in determining which women with a single, prior VTE can be managed without antepartum thromboprophylaxis. In the only credible study of its type, Brill-Edwards and colleagues followed 125 women with a single prior VTE without using heparin thromboprophylaxis during the pregnancy. (Readers should take careful note that all subjects were treated with postpartum anticoagulation for 6 weeks.) All subjects were tested for FVLM, PGM, protein C deficiency and protein S deficiency, antithrombin deficiency, and antiphospholipid antibodies. Some subjects were tested for protein S deficiency during pregnancy, and a free protein S level of less than 24% was considered to indicate protein S deficiency. Overall, 2.5% of the subjects had an antepartum thrombosis. However, none of 44 women who (1) tested negative for thrombophilias and (2) had their prior thrombosis in association with a temporary risk factor, including pregnancy or oral contraceptives, had a recurrent VTE during the antepartum period. Although not all experts agree, these results can be interpreted to allow selected women to avoid antepartum thromboprophylaxis. However, it must be kept in mind that the number of women in this subgroup was too small to conclude that there is no risk of VTE in these women.

In this light, and though the evidence is by no means robust, a reasonable approach to the woman with a single prior VTE episode who has not been tested for thrombophilias and is considering pregnancy or is in early pregnancy is as follows:

- Rule out antiphospholipid syndrome, as this diagnosis would alter pregnancy care as well as be an indication for heparin use.
- In the infrequent circumstance of a family history of antithrombin deficiency, test for antithrombin deficiency, as this diagnosis would be an indication for anticoagulation during pregnancy.
- As a general rule, there is no need for heritable thrombophilia testing in a woman whose single prior VTE was truly idiopathic in nature, that is, not associated with a temporary risk factor (including pregnancy or oral contraceptives), because current evidence suggests the patient should be treated with thromboprophylaxis regardless of the results of heritable thrombophilia testing.
- If after counseling regarding the risks of VTE in pregnancy, the patient with a single prior VTE episode associated with a transient risk factor and who is not on long-term anticoagulants would like to avoid using heparin during pregnancy (antepartum thromboprophylaxis), it is reasonable to do so if she is negative for FVL, PGM, protein C and protein S deficiency (<24% free protein S), antithrombin deficiency, and antiphospholipid antibodies. However, if the patient views antepartum heparin use in her best interest, thrombophilia testing is unnecessary.
The fourth category of patients, those with a family history of VTE but without a personal history of VTE, is particularly difficult. The ACOG admits this when they state “it is controversial whether to test women who do not have a history of thrombosis but have a family history of thrombosis.” Patients with a first-degree relative with antithrombin deficiency should certainly be tested for the same. It would also seem reasonable to test women with a first-degree relative with homozygosity for FVLM or PGM or compound heterozygosity for FVLM and PGM for these mutations.

If thrombophilia screening is deemed necessary, the authors suggest testing for the thrombophilias shown in Box 1. The preferred method for testing for each is also shown. Deciding whether to modify the list of tests ordered should be based on the clinical scenario of each patient and the potential impact on thromboprophylaxis treatment. It is also important that normal physiologic changes in the hemostatic system during pregnancy can alter results for protein C and S testing. Physicians should be aware that testing for antithrombin, and proteins C and S might have falsely low results in the setting of anticoagulant therapy or significant clotting.

THROMBOPROPHYLAXIS

Heparin is the anticoagulant drug of choice during pregnancy. Heparin does not cross the placenta and is widely considered safe for the embryo-fetus. Of the 2 clinically available forms, the low molecular weight heparin (LMWH) preparations offer some advantages over unfractionated heparin (UFH). Both UFH and LMWH act primarily by binding to antithrombin to catalyze the molecule binding to and altering the activity of serine protease procoagulants. UFH enhances the activity of antithrombin for Factor Xa and thrombin, whereas the predominant effect of LMWH is via antithrombin-mediated anti-Factor Xa activity.

UFH has complex pharmacokinetics that ultimately leads to a somewhat unpredictable anticoagulant response. Also, the bioavailability of the UFH after subcutaneous (SC) injection is reduced compared with intravenous infusion. LMWH, in contrast, is less likely to bind nonspecifically to various circulating protein or cell surfaces and so has improved pharmacokinetics and bioavailability when given SC. In addition, LMWH is less likely than UFH to cause heparin-induced thrombocytopenia (HIT) and osteoporosis, though the latter is very infrequent in women treated during pregnancy. For the most part, the longer half-life of LMWH is seen as an advantage because it allows once- or twice-daily dosing regimens to be used.

Box 1
Thrombophilia testing

- Lupus anticoagulant and anticardiolipin antibodies (personal history of VTE only)
- Factor V Leiden mutation
- Prothrombin G20210A mutation
- Antithrombin activity levels
- Protein C activity levels
- Protein S activity levels
Most experts prefer postpartum thromboprophylaxis be accomplished with warfarin, though LMWH is also considered acceptable. Like the heparin compounds, warfarin is regarded as safe for breastfeeding.

The most highly regarded guidelines for pregnancy thromboprophylaxis are those of the American College of Chest Physicians (eighth edition), and the recommendations provided herein are in agreement with these except where specifically noted. The guidelines specifically define UFH, LMWH, and warfarin regimens, as detailed in Table 3.

**General Categories of At-risk Patients**

In an effort to provide a simple and clinically acceptable approach for the obstetrician, the authors suggest that women being considered for thromboprophylaxis be categorized into different clinical scenarios as follows:

- Acute VTE within several months of conception or during pregnancy
- Recurrent VTE (2 or more prior VTEs)
- Single, prior VTE episode and not on long-term anticoagulants
  - Without transient risk factor
  - With transient risk factor
- Antiphospholipid syndrome without prior VTE (diagnosed because of obstetric event(s))
- High-risk thrombophilia
- Low-risk thrombophilia without prior VTE.

**Table 3**

<table>
<thead>
<tr>
<th>Thromboprophylaxis regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unfractionated heparin (UFH)</strong></td>
</tr>
<tr>
<td>Prophylactic UFH</td>
</tr>
<tr>
<td>Intermediate-dose UFH</td>
</tr>
<tr>
<td>Adjusted-dose UFH</td>
</tr>
<tr>
<td><strong>Low molecular weight heparin (LMWH)</strong></td>
</tr>
<tr>
<td>Prophylactic LMWH</td>
</tr>
<tr>
<td>Intermediate-dose LMWH</td>
</tr>
<tr>
<td>Adjusted-dose LMWH</td>
</tr>
<tr>
<td><strong>Postpartum anticoagulation</strong></td>
</tr>
<tr>
<td>Warfarin</td>
</tr>
<tr>
<td>Prophylactic LMWH</td>
</tr>
</tbody>
</table>

*Abbreviations: INR, international normalized ratio; SC, subcutaneously.

* Enoxaparin used as an example; may use other formulations of LMWH.

Acute VTE within several months of conception or during pregnancy
Such patients should be fully anticoagulated with an adjusted-dose UFH or LMWH regimen (see Table 3) for at least 6 months from the initial presentation with VTE. Women who are on warfarin should discontinue the warfarin before 6 weeks of gestation. Some clinicians favor discontinuing the warfarin when the patient initiates attempting to conceive, replacing it with UFH or LMWH.

If the patient reaches 6 months of anticoagulation during the pregnancy, consideration of reducing the degree of anticoagulation (eg, to prophylactic UFH or LMWH) is reasonable, especially in preparation for epidural anesthesia. Following delivery, the UFH or LMWH should be restarted and bridged to warfarin.

Recurrent VTE (2 or more prior VTEs)
Such patients should be fully anticoagulated during pregnancy using an adjusted-dose regimen (see Table 3). Following delivery, the UFH or LMWH should be restarted and bridged to warfarin.

Single, prior VTE episode and not on long-term anticoagulants
Patients whose single, prior VTE occurred without provocation should receive either prophylactic or intermediate-dose UFH or LMWH during pregnancy (see Table 3). Patients whose single, prior VTE was associated with a transient risk factor and who do not have a thrombophilia are candidates to avoid treatment during pregnancy, but must be cautioned regarding the signs and symptoms of VTE and what measures to take to decrease risk. In addition, the physician must take the entire clinical picture, for example, obesity or bed rest, into account. Patients with a single, prior VTE should be given postpartum thromboprophylaxis.

Antiphospholipid syndrome without prior VTE
Women without prior VTE and diagnosed with antiphospholipid syndrome because of pregnancy morbidity should receive either prophylactic or intermediate-dose UFH or LMWH during pregnancy. In the setting of definite antiphospholipid syndrome, the authors and others have suggested prophylactic UFH be 7500 to 10,000 units SC every 12 hours and LMWH to be given in an every 12-hour regimen. Following delivery, postpartum thromboprophylaxis with warfarin or LMWH is indicated.

High-risk thrombophilia
Though uncommon, antithrombin deficiency, homozygosity for FVLM or PGM, heterozygosity for FVLM and PGM, and persistent positive antiphospholipid antibodies are considered by most experts as being at high risk for thrombosis during pregnancy even if the patient has not previously had a VTE. The American College of Chest Physicians guidelines recommends more aggressive management than with other thrombophilies and careful clinical surveillance for VTE. Prophylactic-dose UFH or LMWH may be employed during pregnancy with pharmacologic postpartum thromboprophylaxis. The authors are skeptical regarding the efficacy of prophylactic-dose UFH or LMWH in women with antithrombin deficiency, and favor either intermediate-dose or adjusted-dose UFH or LMWH (with anti-Factor Xa levels monitored). Some women with antithrombin deficiency may need antithrombin concentrate during the pregnancy or peripartum period.

Low-risk thrombophilia without prior VTE
Women without a prior VTE who have heterozygosity for FVLM or PGM, protein C deficiency, or protein S deficiency can be managed without antepartum thromboprophylaxis if an individualized risk assessment proves acceptable. The role of postpartum thromboprophylaxis also will have to be individualized. Regarding the ACOG, specific
treatment recommendations are not made for the asymptomatic patients with low-risk thrombophilia.\textsuperscript{26}

**Cesarean delivery**

Cesarean delivery has been cited as a risk for VTE.\textsuperscript{3,21} Recommendations for thromboprophylaxis are made by Bates and colleagues\textsuperscript{32} for women following cesarean section. It is suggested that those with one additional risk factor (such as those in Table 1) in addition to pregnancy and cesarean delivery receive thromboprophylaxis with prophylactic LMWH or UFH, or by mechanical prophylaxis with lower extremity compression devices while hospitalized. For those with multiple risk factors, both pharmacologic and mechanical prophylaxis should be employed for the same duration of time. Patients with persistent risk factors for VTE following cesarean delivery should have pharmacologic prophylaxis extended for 4 to 6 weeks following delivery. The authors agree with these recommendations.

**Peripartum Heparin Management**

Heparin management during the peripartum period is important to understand, as the risk of hemorrhage is compounded by anticoagulation. Low- to moderate-risk patients on LMWH can be transitioned to UFH at 36 to 37 weeks’ gestation in an effort to improve the likelihood of epidural anesthesia if preterm labor occurs. Patients should be advised that if they suspect spontaneous labor, heparin should be discontinued. For induction or scheduled cesarean, adjusted-dose heparin and intermediate-dose LMWH should be discontinued 24 hours before the scheduled admission. Prophylactic heparin should be discontinued at least 12 hours prior. For high-risk patients, for example, those with a recent VTE, reasonable options include reducing the heparin dose to 5000 units SC twice a day or using a judiciously applied continuous infusion of heparin during labor, with discontinuation when delivery is estimated to be 1 to 2 hours away.

In most cases, heparin should be restarted 6 to 8 hours following delivery or cesarean section. Regarding high-risk patients, continuous infusion should be restarted after delivery when the risk of bleeding has decreased (usually 2 to 4 hours after delivery).

The American Society of Regional Anesthesia (ASRA) has made recommendations regarding anticoagulation and regional anesthesia. Regional anesthesia is contraindicated in patients less than 24 hours from their last dose of twice-daily LMWH. For prophylactic LMWH, regional anesthesia can be placed 10 to 12 hours’ duration from the last dose of LMWH heparin. The neuraxial catheter should be removed 2 hours before the first LMWH dose. Intravenous heparin can be initiated 1 hour following neuraxial anesthesia, with catheter removal 2 to 4 hours after the last heparin dose. SC heparin dosed twice daily with a total dose less than 10,000 units of UFH per day is not a contraindication to neuraxial anesthesia. However, neuraxial anesthesia at doses greater than 10,000 units of UFH or dosing at a frequency greater than twice-daily dosing has not been established to be safe.\textsuperscript{35}

**SUMMARY**

It is evident that obstetricians and gynecologists have the capacity to be uniquely instrumental in the prevention of VTE in the obstetric patient. Attaining the ability to identify patients at risk for VTE, determine who is a candidate for thrombophilia screening, and who may warrant thromboprophylaxis is important to this end. In addition, it is valuable to understand various thromboprophylaxis regimens and peripartum anticoagulant management, as detailed in this review.
REFERENCES