



# Pregnancy-associated thrombosis

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The main reason for the increased risk of thromboembolism in pregnancy is hypercoagulability, which has likely evolved to protect women from the bleeding challenges of miscarriage and childbirth. Women are at a 4- to 5-fold increased risk of thromboembolism during pregnancy and the postpartum period compared with when they are not pregnant. Eighty percent of the thromboembolic events in pregnancy are venous, with an incidence of 0.49 to 1.72 per 1000 pregnancies. Risk factors include a history of thrombosis, inherited and acquired thrombophilia, maternal age greater than 35, certain medical conditions, and various complications of pregnancy and childbirth. Despite the increased risk of venous thromboembolism (VTE) during pregnancy and the postpartum period, most women do not require anticoagulation. Candidates include women with current VTE, a history of VTE, thrombophilia and a history of poor pregnancy outcome, or risk factors for postpartum VTE. The intensity of the anticoagulation will depend on the indication and the monitoring will depend on the intensity. At the time of delivery, anticoagulation should be manipulated to reduce the risk of bleeding complications while minimizing the risk of thrombosis. There are no large trials of anticoagulants in pregnancy, and recommendations are based on case series, extrapolations from nonpregnant patients and the opinion of experts. Nonetheless, anticoagulants are believed to improve the outcome of pregnancy for women who have, or have had, VTE.

Normal pregnancy is accompanied by increased concentrations of factors VII, VIII, X and von Willebrand factor and by pronounced increases in fibrinogen. Factors II, V and IX are relatively unchanged. Free protein S, the active, unbound form, is decreased during pregnancy. Plasminogen activator inhibitor type 1 (PAI-1) levels are increased fivefold. Levels of PAI-2, produced by the placenta, increase dramatically during the third trimester. Markers of thrombin generation such as prothrombin F1 + 2 and thrombin-antithrombin (TAT) complexes are also increased. These changes, which may not completely return to baseline until more than 8 weeks postpartum, begin with conception and result in the hypercoagulable state of pregnancy.<sup>1,2</sup>

The hypercoagulability of pregnancy has likely evolved to protect women from hemorrhage at the time of miscarriage or childbirth. Indeed, in the developing world, the leading cause of maternal death is still hemorrhage,<sup>3</sup> but in Western Europe and the United States, where hemorrhage is successfully treated or prevented, the leading cause of maternal death is thromboembolic disease.<sup>4</sup>

## Epidemiology of Pregnancy-associated Thrombosis

In women who are pregnant, compared with women who are not pregnant, the risk of both arterial and venous throm-

boembolic events is increased. Approximately 20% of these events are arterial and the other 80% are venous.<sup>5</sup> During pregnancy, the risk of venous thromboembolism (VTE) is increased 4- to 5-fold.<sup>6,7</sup> While the risk of VTE may be higher in the third than in the first and second trimesters,<sup>7</sup> an increased risk of VTE is clearly present from the first trimester,<sup>8,9</sup> even before many of the anatomic changes of pregnancy take place. Compared to pregnancy, the risk of VTE is even higher postpartum. During the first 6 weeks postpartum, the risk is 20- to 80-fold higher<sup>6,7</sup> and in the first week, the risk is 100-fold higher.<sup>6</sup> The reported incidence in the last decade, depending on the country and the methods of ascertainment, range from 0.49 to 1.72 per 1000 deliveries.<sup>5,10-14</sup> VTE accounts for 1.1 deaths per 100,000 deliveries,<sup>5</sup> or 10% of all maternal deaths.

Seventy-five percent to 80% of pregnancy-associated VTE is deep vein thrombosis (DVT) and 20% to 25%<sup>5,13</sup> is pulmonary embolism (PE). Half of these venous thromboembolic events occur during pregnancy and half postpartum.<sup>5,14</sup> When DVT occurs during pregnancy, it is more likely to be proximal,<sup>15</sup> massive<sup>15</sup> and in the left lower extremity.<sup>8,9</sup> Distal thromboses are as likely to occur on the right as on the left, but proximal thromboses occurring under the influence of estrogen<sup>16,17</sup> are more likely to be on the left. This left-sided predominance is thought to be due to a relative stenosis of the left common iliac vein, where it

lies between the lumbar vertebral body and the right common iliac artery, but the true mechanism is unknown. Pelvic vein thromboses, which account for less than 1% of all cases of DVT confirmed by venous ultrasound,<sup>18</sup> are rare outside of pregnancy or pelvic surgery, yet account for approximately 10% to 12% of DVT during pregnancy and the postpartum period.<sup>8</sup> Two percent of pregnancy-associated DVT occurs in the upper extremity,<sup>8</sup> but the cases of DVT occurring in association with assisted reproductive technologies occur predominantly in the upper extremity or neck in women whose pregnancies are complicated by the ovarian hyperstimulation syndrome.<sup>14,19</sup>

### Risk Factors for Venous Thromboembolism in Pregnancy

The physiological changes, besides hypercoagulability, that accompany pregnancy and childbirth such as hormonally induced increased venous capacitance and decreased venous outflow,<sup>20,21</sup> mechanical obstruction by the uterus,<sup>22</sup> decreased mobility<sup>23-26</sup> and vascular injury<sup>22</sup> are likely important factors in the development of pregnancy-associated VTE.

The most important individual risk factor for VTE in pregnancy is a history of thrombosis. Fifteen percent to 25% of thromboembolic events in pregnancy are recurrent events. The risk of recurrent VTE in pregnancy is also increased 3-to 4-fold (relative risk 3.5 [95% confidence interval 1.6, 7.8]).<sup>27</sup> In recent studies, the rate of recurrent VTE in women who did not receive anticoagulation has been reported to range from 2.4% to 12.2%.<sup>28-30</sup> In women who did receive anticoagulation, the rate of recurrent VTE has been reported to range from 0% to 2.4%.<sup>28,31,32</sup>

Besides a history of thrombosis, the most important individual risk factor for VTE in pregnancy is thrombophilia.<sup>5,8</sup> Thrombophilia is present in 20% to 50%<sup>2</sup> of women who experience VTE during pregnancy and the postpartum period. Both acquired and inherited thrombophilia increase the risk. The risk of VTE conferred by type of thrombophilia was systematically reviewed by Robertson et al<sup>33</sup> and is summarized in **Table 1**. The odds ratios for thrombophilias that have traditionally been thought of as high risk, such as deficiencies of protein C, protein S and antithrombin, are lower than might be expected given early reports.

In the last decade, several large population-based studies have identified other patient characteristics, medical conditions and complications that increase the risk of pregnancy-associated VTE.<sup>5,12-14,23,34</sup> The odds ratios and confidence intervals for these risk factors are summarized in **Table 2**. In general, the patient characteristics and medical conditions that are risk factors for VTE in the general population are risk factors for pregnancy-associated VTE.

### Indications for Anticoagulation During Pregnancy

Despite the increased risk of VTE during pregnancy and the postpartum period, most women do not require anticoagulation. In most cases, the risks of anticoagulation outweigh its benefits. Women who would benefit from anticoagulation for prevention of thrombosis in pregnancy are those whose risk of VTE is greater than the risk of bleeding complications from heparin or low-molecular-weight heparin, which has been reported to be as high as 2%.<sup>31,32,35,36</sup> Women who would benefit are those with a history of thrombosis.

Other women who may benefit from anticoagulation in pregnancy are women with inherited or acquired thrombophilia and a history of poor pregnancy outcome. In the antiphospholipid syndrome, several studies have demonstrated that anticoagulation with heparins improves the outcome of pregnancy,<sup>37</sup> and in inherited thrombophilia, case reports, case series and one small randomized trial<sup>38</sup> have also suggested that anticoagulation with heparins can improve the outcome of pregnancy. Large studies, however, have not been conducted. It is also possible, however, that anticoagulation with heparins can improve the outcome of pregnancy in women with a history of placenta-mediated complications of pregnancy whether or not they have thrombophilia, as suggested by a recently completed randomized trial using dalteparin in such women.<sup>39</sup>

Ideally, evaluation of the woman who may require anticoagulation during pregnancy should occur prior to conception, or at least early in pregnancy. Women with conditions that place them at a high risk of maternal mortality due to thrombosis should be counseled against pregnancy. These conditions include mechanical heart valves, chronic thromboembolic pulmonary hypertension, a history of recurrent thrombosis while fully anticoagulated and a history of myocardial infarction. Most women with a history

**Table 1. Risk of venous thromboembolism (VTE) conferred by type of thrombophilia.<sup>33</sup>**

Thrombophilia	Odds Ratios (95% CI)
Factor V Leiden – homozygosity	34.40 (9.86, 120.05) <sup>33</sup>
Factor V Leiden – heterozygosity	8.32 (5.44, 12.70) <sup>33</sup>
Prothrombin gene mutation – homozygosity	26.36 (1.24, 559.29) <sup>33</sup>
Prothrombin gene mutation – heterozygosity	6.80 (2.46, 18.77) <sup>33</sup>
Protein C deficiency	4.76 (2.15, 10.57) <sup>33</sup>
Protein S deficiency	2.19 (1.48, 6.00) <sup>33</sup>
Antithrombin deficiency	4.76 (2.15, 10.57)
Methylene tetrahydrofolate reductase C677T – homozygosity	0.74 (0.22, 2.48) <sup>33</sup>
Antiphospholipid antibodies	15.8 (10.9, 22.8) <sup>5</sup>

**Table 2. Medical conditions and complications of pregnancy and delivery associated with an increased risk of venous thrombosis in pregnancy.**

	Lindqvist et al <sup>12</sup>	Danilenko-Dixon et al <sup>23</sup>	Simpson et al <sup>13</sup>	James et al <sup>5</sup>	Larsen et al <sup>34</sup>	Jacobsen et al <sup>14</sup>
Odds ratios and 95% confidence intervals						
<b>Patient Characteristics</b>						
Age > 35	1.3 (1.0, 1.7)	–	1.5 (1.1, 2.2)	1.4 (1.2, 1.8)	–	–
Nulliparity	1.8 (1.2, 2.7)	0.9 (0.37, 2.2)	–	–	–	1.7 (1.3, 2.3) antenatal
Para 2	1.5 (1.1, 1.9)	–	–	–	–	0.8 (0.5, 1.2) antenatal
Para ≥ 2	–	–	–	–	–	–
Para ≥ 3	2.4 (1.8, 3.1)	–	–	–	–	1.9 (1.2, 3.0) postnatal
African-American race	–	–	–	1.4 (1.2, 1.6)	–	–
<b>Medical Conditions</b>						
Heart disease	–	–	5.1 (2.5, 10.5)	7.1 (6.2, 8.3)	–	–
Sickle cell disease	–	–	–	6.7 (4.4, 10.1)	–	–
Systemic lupus erythematosus	–	–	–	8.7 (5.8, 13.0)	–	–
Obesity	–	–	–	4.4 (3.4, 5.7)	5.3 (2.1, 13.5) BMI >30	–
Diabetes	–	–	–	2.0 (1.4, 2.7)	–	–
Hypertension	–	–	–	1.8 (1.4, 2.3)	–	–
History of superficial thrombophlebitis	–	10.0 (1.3, 78)	–	–	–	–
Smoking for ≥ 10 per day	1.4 (1.1, 1.9)	2.5 (1.3, 4.7)	–	1.7 (1.4, 2.1)	2.7 (1.5, 4.9)	–
<b>Complications of Pregnancy and Delivery</b>						
Assisted reproduction	–	–	–	–	–	4.4 (2.6, 7.5) antenatal
Multiple gestation	1.8 (1.1, 3.0)	7.0 (0.36, 135)	–	1.6 (1.2, 2.1)	–	2.7 (1.6, 4.5) antenatal
Hyperemesis	–	–	–	2.5 (2.0, 3.2)	–	–
Gestational diabetes	–	–	–	–	–	4.0 (2.0, 8.9) antenatal
Antepartum hemorrhage	–	–	–	2.3 (1.8, 2.8)	–	–
Preeclampsia	2.9 (2.1, 3.9)	1.0 (0.15, 7.1)	–	0.9 (0.7, 1.0)	–	3.8 (2.8, 5.1) postnatal
Cesarean delivery	3.6 (3.0, 4.3)	1.2 (0.9, 1.5)	2.6 (1.9, 3.4)	2.1 (1.8, 2.4)	–	2.7 (1.8, 4.0) planned 4.0 (3.0, 5.3) emergency
Postpartum infection	–	–	–	4.1 (2.9, 5.7)	–	–
Postpartum hemorrhage	–	9.0 (1.1, 71)	–	1.3 (1.1, 1.6)	–	–
Transfusion	–	5.0 (0.58, 43)	–	7.6 (6.2, 9.4)	–	–

of VTE, however, can be counseled that their risks are manageable and are probably reduced with anticoagulation.

### Using Anticoagulation to Prevent VTE During Pregnancy

Women who are already on full anticoagulation will likely need to continue. They should be counseled about the harmful effects of warfarin on the fetus and offered the opportunity to be converted to low-molecular-weight heparin prior to conception. Women who have not had a complete thrombophilia work-up may be tested. While the results of thrombophilia testing will not alter the general recommendation for anticoagulation in pregnancy, the results may alter the dose intensity from low or “prophylactic” to full, weight-based, adjusted-dose or “therapeutic.”

Although some experts would recommend thromboprophylaxis for all pregnant women with inherited thrombophilia, anticoagulation is probably not necessary if there is no personal history of thromboembolism or poor pregnancy outcome.<sup>40</sup> The exceptions may be women with additional risk factors, including women with multiple thrombophilias.

Unique aspects of anticoagulation in pregnancy include both maternal and fetal issues. Warfarin, the preferred agent for long-term anticoagulation outside of pregnancy, has harmful fetal effects. Warfarin taken during the critical period for organogenesis, the 4<sup>th</sup> to the 8<sup>th</sup> week after conception, is associated with a 15% to 56% reported risk of miscarriage and, depending on the case series, carries up to a 30% risk of congenital anomalies. Placental transfer of warfarin later in pregnancy can result in fetal bleeding or stillbirth. Long-term sequelae include an increased risk of adverse neurologic outcome.<sup>41</sup>

The preferred agents for anticoagulation in pregnancy are heparin compounds. Neither heparin nor low-molecular-weight heparin crosses the placenta and both are considered safe in pregnancy. Unique aspects of anticoagulation with heparins in pregnancy include an increase in maternal blood volume of 40% to 50% and an increase in the volume of distribution. An increase in glomerular filtration results in increased renal excretion of heparin compounds, which are eliminated by this route. Additionally, there is an increase in protein binding of heparin.<sup>41</sup> During pregnancy, both unfractionated heparin and low-molecular-weight heparins have shorter half-lives and lower peak plasma concentrations, usually necessitating higher doses and more frequent administration in order to maintain peak concentrations.<sup>2</sup>

Disadvantages of unfractionated heparin include the necessity of parenteral administration, a risk of major bleeding, a risk of reduced bone density, a risk of vertebral fracture and a risk of

heparin-induced thrombocytopenia (HIT).<sup>41</sup> While the risk of HIT is low in pregnancy and may be lower than in nonpregnant patients, the actual risk is unknown.<sup>40</sup>

There are few comparative studies in pregnancy, but in nonpregnant patients, low-molecular-weight heparin has been associated with fewer side effects than unfractionated heparin.<sup>40</sup> Potential advantages of low-molecular-weight heparin are less bleeding, a more predictable response, a lower risk of HIT (no cases were confirmed in two large reviews of the use of low-molecular-weight heparin in pregnancy<sup>31,36</sup>), a longer half-life and less bone loss.<sup>42</sup> However, in a randomized trial of low-dose unfractionated heparin versus enoxaparin for thromboprophylaxis in pregnancy, there was no difference in the incidence of clinically significant bone loss (which was 2%-2.5%) between women who took unfractionated heparin compared to those who took enoxaparin.<sup>43</sup> Two studies have found that postpartum bone mineral density in women who took low-dose low-molecular-weight heparin throughout pregnancy was no different than postpartum bone mineral density in untreated controls.<sup>44,45</sup> An advantage of enoxaparin, and probably other low-molecular-weight heparins as well, is less bruising at injection sites.<sup>46</sup> A disadvantage of low-molecular-weight heparins, besides their cost, is their longer half-life, which is an issue at the time of delivery.

There are no large trials of anticoagulants in pregnancy, and recommendations for their use are based on case series and the opinion of experts. Full-dose (adjusted dose) anticoagulation is recommended<sup>40,47</sup> for women with either a need for life-long anticoagulation or antiphospholipid syndrome with a history of thrombosis. For women with a history of unprovoked thrombosis who are not on life-long anticoagulation, while the *Chest* guidelines recommend either low-dose anticoagulation or close observation with postpartum prophylaxis,<sup>40</sup> we recommend low-dose anticoagulation. More aggressive therapy (intermediate or moderate dose) is recommended<sup>40</sup> for women with a history of unprovoked thrombosis who are not on life-long anticoagulation but who have antithrombin deficiency or homozygosity for the factor V Leiden mutation, the prothrombin gene G20210A mutation, or compound heterozygosity for both mutations. Regimens from the *Chest* guidelines and our protocol are included in **Table 3**. Any adjustment for obesity is incorporated into the full, weight-based, adjusted-dose or “therapeutic” regimens. We do not have a formal protocol for adjusting low, moderate or “prophylactic” doses in women who are obese, but we do make adjustments on a case-by-case basis.

In one series, women with a history of thrombosis in the setting of transient risk factors had a rate of recurrence in

**Table 3. Protocols for thromboprophylaxis in pregnancy.**<sup>40,55</sup>

	Bates et al 2008 <sup>40</sup>	Duke Protocol <sup>55</sup>
<b>Unfractionated heparin</b>		
Mini-dose "low dose" "prophylactic dose"	<ul style="list-style-type: none"> <li>5000 U sc q 12 hrs</li> </ul>	<ul style="list-style-type: none"> <li>5000 U sc q 12 hrs &lt; 8 weeks</li> <li>7500 U sc q 12 hrs 8-28 weeks</li> <li>10,000 U sc q 12 hrs &gt; 28 weeks</li> </ul>
Intermediate (moderate) dose "low dose"	<ul style="list-style-type: none"> <li>q 12 hrs to target anti-factor Xa level of 0.1-0.3 U/mL</li> </ul>	
Adjusted dose "full dose"	<ul style="list-style-type: none"> <li>q12 hrs to target mid-interval aPTT in therapeutic range</li> </ul>	<ul style="list-style-type: none"> <li>q 8 or 12 hrs to target mid-interval aPTT in therapeutic range</li> </ul>
<b>Low-molecular-weight heparin</b>		
Prophylactic dose or "low dose"	<ul style="list-style-type: none"> <li>Enoxaparin 40 mg qd</li> <li>Dalteparin 5000 U qd</li> <li>Tinzaparin 4500 U qd</li> </ul>	<ul style="list-style-type: none"> <li>Enoxaparin 40 mg qd or 30 mg bid before 28 weeks then</li> <li>Enoxaparin 40 mg bid after 28 weeks</li> </ul>
Intermediate or moderate dose	<ul style="list-style-type: none"> <li>Dalteparin 5000 U q 12 hrs or</li> <li>Enoxaparin 40 mg q 12 hrs</li> </ul>	
Weight-adjusted dose "full dose"	<ul style="list-style-type: none"> <li>Enoxaparin 1 mg/kg bid</li> <li>Dalteparin 100 U/kg q 12 hrs or 200 U/kg q 24 hrs</li> <li>Tinzaparin 175 mg U/kg qd</li> </ul>	<ul style="list-style-type: none"> <li>Enoxaparin 1 mg/kg bid with target of anti-factor Xa level of 0.5-1.0 with monthly levels</li> </ul>

pregnancy similar to that of other women with a history of thrombosis,<sup>29</sup> but close observation (assessment of signs and symptoms of thrombosis at routine prenatal visits) may be an option for women with a history of thrombosis in the setting of transient risk factors such as injury or immobility.<sup>40</sup> Nonetheless, if these women do not receive anticoagulation during pregnancy, they should be considered for thromboprophylaxis postpartum.

At the present time there are insufficient data to justify the routine use of fondaparinux, as opposed to heparins, for prophylaxis of VTE in pregnancy. Nonetheless, if danaparoid is unavailable, fondaparinux is probably the anticoagulant of choice in cases of severe cutaneous allergies or HIT in pregnancy.<sup>48,49</sup>

### Diagnosing and Managing New VTE

The two most common initial symptoms, present in more than 80% of women with pregnancy-associated DVT, are pain and swelling in an extremity.<sup>8</sup> When signs or symptoms suggest new onset DVT, the recommended initial diagnostic test is compression ultrasonography of the proximal veins.<sup>40</sup> When results are negative and iliac vein thrombosis is not suspected, compression ultrasonography can be repeated in 3 days. When results are negative or equivocal and an iliac vein thrombosis is suspected, magnetic resonance direct thrombus imaging may be used.<sup>50</sup> D-dimer testing with currently available assays has not been helpful in excluding VTE, as pregnancy is accompanied by an increase in D-dimer levels and a high proportion of false positive results.

The diagnosis of new onset PE is similar to that in the nonpregnant individual, as the optimal diagnostic strategy in pregnancy is yet to be determined. Both ventilation/perfusion (V/Q) scanning and computed-tomographic angiography (CT angiography) give relatively low radiation exposure to the fetus.<sup>50</sup> There are concerns, however, about maternal radiation exposure with CT angiography. Estimates of radiation absorption by maternal breast tissue are 10 mGy compared with 0.28 mGy for a V/Q scan and each 1 mGy of radiation exposure is associated with an increase of breast cancer by an additional 1 in 50,000 women.<sup>50</sup> A risk of this small magnitude must be weighed against the potential consequences of withholding CT angiography and failing to make a proper diagnosis. A recent study concluded that a chest X-ray could be used as a discriminator to reduce the likelihood of nondiagnostic test results and increase the likelihood of diagnostic test results in the evaluation of pregnancy-associated PE. Pregnant women with a negative chest X-ray were more likely to have a diagnostic test result with a V/Q scan, and pregnant women with an abnormal chest X-ray were more likely to have a diagnostic test result with CT angiography.<sup>51</sup>

In nonpregnant patients with DVT, hospital admission is frequently not necessary, but pregnant patients, who tend to have large clots, are usually admitted. While low-molecular-weight heparin is sometimes used for the initial treatment of PE, it has not been as well studied in this situation. An advantage of intravenous unfractionated heparin over low-molecular-weight heparin in the initial treatment of PE is that the infusion can be turned off, allowing the heparin to clear in a few hours. This may be important in situations

where delivery, surgery or thrombolysis (indicated for life- or limb-threatening thromboembolism) may be necessary. When patients appear to be stable, they are usually switched from intravenous unfractionated heparin to low-molecular-weight heparin and can be discharged from the hospital.

### Monitoring Anticoagulation During Pregnancy

It is not clear whether the dose of low-molecular weight heparin needs to be adjusted, when used in full, weight-based, adjusted-dose or “therapeutic” intensity to treat or prevent VTE. On the basis of small studies demonstrating the need for increased low-molecular-weight heparin to maintain anti-factor Xa levels in the 0.6 to 1.0 U/mL range, some advocate the performance of periodic (every 1 to 3 months) anti-factor Xa levels 4 to 6 hours after injection, but other studies have shown that few women actually require increased doses when low-molecular-weight heparin is used.<sup>40</sup> It is our practice to obtain an anti-factor Xa level approximately 4 hours after injection within the first week of starting therapy and then repeat the level monthly at routine prenatal visits, adjusting the level upward or downward as necessary. When patients are converted to unfractionated heparin in the last month of pregnancy, we check an activated partial thromboplastin time (aPTT) once or twice a week and adjust their dose of heparin to maintain the mid-dose aPTT at the lower end of the therapeutic range.

Patients receiving low-intensity anticoagulation should not need any monitoring, but our protocol calls for us to check an anti-factor Xa level or aPTT 1 week after starting therapy or making a dose change. The purpose is to make sure we are not overly anticoagulating a patient.

The *Chest* guidelines recommend platelet counts every 2 or 3 days during the first two weeks of unfractionated heparin therapy and do not recommend routine platelet counts in obstetric patients who are receiving only low-molecular-weight heparin.<sup>52</sup> It is our practice to check a platelet count along with an anti-factor Xa level 1 week after starting low-molecular-weight heparin and repeating the platelet count one week later.

### Recommendations for Management Around Delivery

Women on either full- or low-dose anticoagulation may be converted from low-molecular-weight heparin to unfractionated heparin in the last month of pregnancy or sooner if delivery appears imminent. The purpose of converting women to unfractionated heparin, which is shorter acting, has less to do with any risk of bleeding at the time of delivery, but rather with the rare possibility of an epidural or spinal hematoma with regional anesthesia. The

American Society of Regional Anesthesia and Pain Medicine (ASRA) consensus statement on the subject recommends against needle placement within 10 to 12 hours after the last low-molecular-weight heparin dose.<sup>53</sup> Our anesthesiologists will not place a regional anesthetic if a woman has received low-molecular-weight heparin within the past 24 hours. Should a woman go into labor while taking unfractionated heparin, the heparin will usually, but not always, clear within 6 hours. Clearance can be verified by an aPTT. Heparin, however, does have the potential for causing a persistent anticoagulant effect<sup>10</sup> and, therefore, whenever reasonable, should be held 24 hours prior to anticipated delivery or regional anesthetic. Reversal of heparin is rarely required and is not indicated for low-dose heparin.

Although the use of pneumatic compression devices for the prevention of pregnancy-associated thrombosis has not been studied, extrapolating from perioperative data, we suggest placement of pneumatic compression devices in labor or prior to cesarean delivery for women whose anticoagulation has temporarily been discontinued.

### Indications for Anticoagulation During the Postpartum Period

Cesarean delivery at least doubles the risk of VTE, but in the otherwise normal patient, the risk remains low (approximately 1 per 1000). Randomized trials of thromboprophylaxis at the time of cesarean delivery have been small and not adequately powered to assess a decrease in the risk of DVT or PE with anticoagulation, and published decision analyses have substantial limitations. Nonetheless, patients with at least one additional risk factor may be candidates for thromboprophylaxis with pneumatic compression devices, unfractionated heparin or low-molecular-weight heparin.<sup>40</sup> Patients with multiple risk factors for DVT or PE should receive thromboprophylaxis with both pneumatic compression devices and unfractionated heparin or low-molecular-weight heparin.<sup>40</sup> Obviously, any patient receiving thromboprophylaxis during pregnancy will require thromboprophylaxis postpartum.

Additional measures should be considered for certain women at particularly high risk of thrombosis at the time of delivery. Women who have antithrombin deficiency may be candidates for antithrombin concentrates. Women who have had DVT in the previous 2 to 4 weeks may be candidates for vena caval filter placement with removal postpartum.

### Management of Anticoagulation Postpartum

To minimize bleeding complications, resumption of anticoagulation should be postponed until 12 hours after vaginal delivery, 2 to 12 hours after epidural removal, or 24

hours after cesarean delivery. Current recommendations by ASRA are for resumption of prophylactic low-molecular-weight heparin no sooner than 2 hours post epidural removal, but our anesthesiologists ask us to wait 12. Since the optimal interval for resumption of therapeutic anticoagulation post epidural removal is unclear, 12 hours is not unreasonable. Pneumatic compression devices should be left in place until the patient is ambulatory and until anticoagulation is restarted. After the risk of postpartum hemorrhage has decreased, which may be 2 or more weeks after delivery, women who require more than 6 weeks of anticoagulation may be bridged to warfarin, which is compatible with breastfeeding. We believe that bridging, and having women on two anticoagulants simultaneously, sooner than 2 weeks postpartum has contributed to delayed postpartum hemorrhages in our patients. For women who require only 6 weeks of anticoagulation postpartum, the utility of warfarin is limited, since it requires 1 to 2 weeks of administration before a therapeutic range is attained. Most of our patients opt to remain on low-molecular-weight heparin for the 6-week period. Women who have experienced VTE during the current pregnancy should probably remain on warfarin for at least another 3 to 6 months after delivery. Estrogen-containing contraceptives are generally contraindicated for women with thrombophilia or a history of thrombosis who are not on anticoagulation, but progestin-only contraceptives have not been found to increase the risk of thrombosis and are, therefore, generally allowed.<sup>54</sup>

## Summary

Women are at an increased risk of VTE during pregnancy. Factors that increase the risk further include a history of thrombosis, thrombophilia, age greater than 35 years, African-American race, certain medical conditions and some complications of pregnancy and childbirth. Despite the increased risk of VTE during pregnancy and the postpartum period, most women do not require anticoagulation. Exceptions are women with a current thrombosis, women with a history of thrombosis, women with thrombophilia and a history of poor pregnancy outcome, and women at high risk for thrombosis postpartum. Unique aspects of anticoagulation in pregnancy include both maternal and fetal issues. For fetal reasons, the preferred agents for anticoagulation in pregnancy are heparin compounds. At the time of delivery, anticoagulation can and should be manipulated to reduce the risk of bleeding complications while minimizing the risk of thrombosis. Postpartum, the risk of thrombosis is higher than it is during pregnancy. Women with multiple risk factors for postpartum VTE should receive prophylactic anticoagulation.

## Disclosures

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Off-label drug use: Anticoagulants and their use to treat and prevent thrombosis in pregnancy.

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