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What is This?
Pregnancy-Related Venous Thromboembolism

Emily M. Armstrong, PharmD, BCACP1,2, Jessica M. Bellone, PharmD, BCACP3, Lori B. Hornsby, PharmD, BCPS1,4, Sarah Treadway, PharmD, BCPS1,5, and Haley M. Phillippe, PharmD, BCPS1,6

Abstract
Pregnancy is associated with an increased risk of venous thromboembolism (VTE), with a reported incidence ranging from 0.49 to 2 events per 1000 deliveries. Risk factors include advanced maternal age, obesity, smoking, and cesarean section. Women with a history of previous VTE are at a 4-fold higher risk of recurrent thromboembolic events during subsequent pregnancies. Additionally, the presence of concomitant thrombophilia, particularly factor V Leiden (homozygosity), prothrombin gene mutation (homozygosity), or antiphospholipid syndrome (APS), increases the risk of pregnancy-related VTE. Low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) are the drugs of choice for anticoagulation during pregnancy. LMWH is preferred due to ease of use and lower rates of adverse events. Women with high thromboembolic risk particularly those with a family history of VTE should receive antepartum thromboprophylaxis. Women with low thromboembolic risk or previous VTE caused by a transient risk factor (ie, provoked), who have no family history of VTE, may undergo antepartum surveillance. Postpartum anticoagulation can be considered in women with both high and low thromboembolic risk.

Keywords
thrombophilia, pregnancy, inherited thrombophilia, acquired thrombophilia, prophylaxis

Introduction
Pregnancy increases the risk of venous thromboembolism (VTE) due to various physiological and anatomical changes. The presence of an underlying thrombophilia, either inherited or acquired, may further increase this risk. Studies reporting a higher risk of VTE during the postpartum period as compared to the antepartum period suggest differences in VTE throughout the course of pregnancy. This review will focus on risk factors associated with VTE in pregnancy as well as considerations for both prophylaxis and treatment of VTE during pregnancy and the postpartum period.

Incidence and Overall Risk
VTE remains one of the leading causes of maternal morbidity and mortality in developed countries, accounting for approximately 10% of pregnancy-related deaths. During pregnancy, there is a 4- to 5-fold increased risk of VTE, with a reported incidence ranging from 0.49 to 2 events per 1000 deliveries. Approximately 80% of cases with pregnancy-associated VTE are due to deep vein thrombosis (DVT) and 20% due to pulmonary embolism (PE). One meta-analysis found two-thirds of DVT occurred during the antepartum period (period before childbirth), while as many as 60% of pregnancy-related PE occur up to 6 weeks postpartum. The risk of VTE begins to increase in the first trimester prior to the anatomic changes associated with pregnancy. Although a higher risk of VTE during the third trimester has been reported, other studies have suggested there is an equal risk of events throughout each trimester. The postpartum risk of VTE exceeds that of the antepartum period. During the first 6 weeks postpartum, the risk of VTE is up to 80-fold higher, with the highest risk occurring during the first week postpartum. Although the rate of

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VTE is approximately 100 per 100,000 woman years during pregnancy, the rate during the postpartum period increases to approximately 500 per 100,000 woman years. In comparison, studies have estimated that the risk of VTE following cesarean section ranges from <1 in 1000 to 18 in 1000 deliveries; however, due to hospital records and disease coding, this risk may be underestimated.

Mechanisms

Physiologic changes during pregnancy produce a hypercoagulable state, which is helpful in maintaining placental function and reducing blood loss at the time of delivery. However, these changes are also thought to contribute to the increased risk of VTE seen during pregnancy. Throughout pregnancy, levels of factors VII, VIII, and X are increased. von Willebrand factor (vWF) has been found to increase progressively through-out pregnancy, while the natural anticoagulants, protein S and tissue plasminogen activator (t-PA), are reduced. There is a high rate of DVT occurrence in the left lower extremity, which is hypothesized to be secondary to compression of the inferior vena cava and pelvic veins from the enlarging uterus. An estrogen-mediated reduction in venous wall smooth muscle tone leads to venous distention, causing an increase in venous stasis in the lower extremities and endothelial disruption in the common femoral vein. Additional endothelial damage to the pelvic veins occurs during delivery, which may contribute to the increased risk of VTE observed postpartum.

Risk Factors

A personal history of VTE is a significant risk factor for VTE during pregnancy. Women with a previous VTE have a 3- to 4-fold increased risk of recurrent events during subsequent pregnancies, with studies demonstrating rates of recurrence of 6% to 8% during the antepartum and postpartum period, respectively. In a prospective study of 125 pregnant women with a previous single episode of VTE, the incidence of antepartum and postpartum recurrence without prophylaxis was 2.4% (95% confidence interval [CI] 0.2%-6.9%) and 2.5% (95% CI 0.5%-7.0%), respectively. Evidence regarding other prognostic factors for recurrent VTE has been conflicting. One post hoc analysis found a low risk of recurrence in women without thrombophilia with a temporary risk factor, including oral contraceptives or pregnancy-related VTE, at the time of their first event. Alternatively, retrospective studies have failed to show a consistent association between temporary risk factors and recurrent VTE. Investigators found women with a first VTE provoked by use of oral contraceptives or related to pregnancy or the postpartum period were at a higher risk of recurrent thromboembolism than those who experienced an episode of VTE provoked by a nonhormonal transient risk factor; it should be noted however that this difference did not reach statistical significance. For women with a history of prior VTE, the American College of Chest Physicians classify risk as low, moderate, or high for recurrent VTE during pregnancy.

Table 1. VTE Risk in Pregnancy With Underlying Thrombophilia.

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden homozygosity</td>
<td>34.40</td>
<td>9.86-120.05</td>
</tr>
<tr>
<td>Prothrombin gene mutation homozygosity</td>
<td>26.36</td>
<td>1.24-559.29</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>15.8</td>
<td>10.9-22.8</td>
</tr>
<tr>
<td>Factor V Leiden heterozygosity</td>
<td>8.32</td>
<td>5.44-12.70</td>
</tr>
<tr>
<td>Prothrombin gene mutation heterozygosity</td>
<td>6.80</td>
<td>2.46-18.77</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>4.76</td>
<td>2.15-10.57</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>4.76</td>
<td>2.15-10.57</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>2.19</td>
<td>1.48-6.00</td>
</tr>
<tr>
<td>Methyltetrahydrofolate reductase C677T mutation homozygosity</td>
<td>0.74</td>
<td>0.22-2.48</td>
</tr>
</tbody>
</table>

Abbreviation: VTE, venous thromboembolism.

Oral Anticoagulants

Women who experience an acute VTE during pregnancy should receive therapeutic doses of anticoagulation throughout pregnancy and up to 6 weeks postpartum, for a total minimum
duration of 3 months. Although warfarin is the drug of choice for long-term management of VTE in most situations, it is considered category X by the Food and Drug Administration due to the teratogenic effects seen in the fetus and infant. Warfarin exposure during the 6th to 10th week of gestation has increased risk of miscarriage, stillbirth, dorsal midline dysplasia, and fetal wastage with warfarin use in pregnancy. Although warfarin is the drug of choice for long-term management of VTE in most situations, does not have data for treatment during pregnancy. Preclinical animal studies have shown that rivaroxaban crosses the placenta and causes maternal hemorrhagic complications, increases fetal toxicity, decreases the number of live fetuses, and reduces fetal body weight. Animal studies have also demonstrated rivaroxaban to be secreted into breast milk and therefore should not be used for VTE treatment in breast-feeding women at this time.

Heparin Compounds

Heparin compounds such as unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) do not cross the placenta and have not been associated with fetal bleeding or teratogenicity; therefore, these agents are the preferred anticoagulants during pregnancy. Additionally, as UFH and LMWH do not accumulate in breast milk, they are considered compatible with breast-feeding. LMWHs have largely replaced UFH for treatment of thromboembolism in pregnancy. In studies of nonpregnant patients, LMWH has been shown to be as safe and efficacious as UFH in the acute treatment of DVT and PE. Other studies in the nonpregnant population have also demonstrated that LMWH is as effective as warfarin in preventing recurrent VTE. LMWH use in 2777 pregnancies was found to be safe and efficacious, with no maternal deaths and an overall rate of VTE of 0.86% (95% CI 0.55%-1.28%). In one Cochran review of pregnancy-related VTE, symptomatic VTE occurred more frequently in women receiving UFH than LMWH; however, the included studies were not powered to detect a statistically significant difference between treatment groups (risk ratio [RR] 0.47, 95% CI 0.09-2.49).

Table 2. Additional VTE Risk Factors in Pregnancy.1,4,5,14

<table>
<thead>
<tr>
<th>Preexisting Risk Factor</th>
<th>Odds Ratio (95% CI) Transient Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history VTE</td>
<td>24.8 (17.1-36.0)</td>
<td>Infection—vaginal delivery</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>6.7 (4.4-10.1)</td>
<td>Postpartum hemorrhage with surgery</td>
</tr>
<tr>
<td>Smoking—postpartum VTE</td>
<td>3.4 (2.0-5.5)</td>
<td>Immobility—postpartum VTE</td>
</tr>
<tr>
<td>Obesity—postpartum VTE</td>
<td>2.4 (1.7-3.3)</td>
<td>Immobility—antepartum VTE</td>
</tr>
<tr>
<td>Smoking—anteprtum VTE</td>
<td>2.1 (1.3-3.4)</td>
<td>In vitro fertilization—twins</td>
</tr>
<tr>
<td>Age &gt; 35 years</td>
<td>2.1 (2.0-2.3)</td>
<td>Infection—any cesarean section</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.0 (1.4-2.7)</td>
<td>Preeclampsia with IUGR</td>
</tr>
<tr>
<td>Obesity—anteprtum VTE</td>
<td>1.8 (1.3-2.4)</td>
<td>Postpartum hemorrhage with surgery</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.8 (1.4-2.3)</td>
<td>Preeclampsia without IUGR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cesarian section</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cesarian section</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emergency without infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twin pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cesarian section</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; VTE, venous thromboembolism.
of LMWH, bone mineral density was significantly lower in patients receiving UFH \((P = 0.02)\), and similar as compared to aspirin or placebo.\(^{41-43}\) Alternatively, 1 trial demonstrated that the incidence of clinically significant bone loss was no different in patients receiving UFH compared to patients taking LMWH \((2.5\% \text{ vs } 2.0\%); P = 1.0)\), which suggests that osteoporosis may be due to individual susceptibility.\(^{27,44}\)

The anticoagulant dose will depend on the indication, with low, intermediate, and treatment doses available for both UFH and LMWH. There are no large clinical trials evaluating the optimal dosing regimens of anticoagulants during pregnancy. Therefore, recommendations are largely based on expert opinion and case series (Table 3).\(^2\) As changes in renal excretion and protein binding occur during pregnancy, the half-lives and peak plasma concentrations of these agents may be altered, requiring a higher dose and/or more frequent administration.\(^2,4\)

Due to these alterations in the pharmacokinetics of LMWH, twice-daily dosing is often recommended.\(^45\) However, data suggest that once-daily dosing of LMWH may be appropriate for VTE treatment.\(^46,47\) Because of small studies indicating the need for LMWH dose escalation to maintain the therapeutic anti-Xa levels, some support monitoring anti-Xa levels every 1 to 3 months to maintain an anti-Xa level of 0.6 to 1.0 units/mL for twice-daily regimens.\(^27,48,49\) However, other studies have shown that few women require an adjustment in LMWH dose when therapeutic doses are used.\(^50,51\) Additional arguments suggesting routine monitoring of anti-Xa levels that may not be necessary in pregnancy include concerns with testing reliability and accuracy, insufficient clinical end points demonstrating an optimal therapeutic anti-Xa range, a lack of data correlating monitoring with risk of bleeding and/or VTE recurrence, and the cost of monitoring.\(^27\) Due to these arguments, it is difficult to justify routine monitoring of anti-Xa levels for the treatment of VTE in pregnancy at this time.

When choosing an anticoagulant in pregnancy, it is important to weigh the advantages and disadvantages of individual agents. Disadvantages of UFH, in addition to the possible need for continuous infusion or intravenous administration with therapeutic doses, include the risk of major bleeding, bone loss, vertebral fracture, and HIT.\(^4\) Potential advantages of LMWH over UFH are lower rates of bleeding, decreased risk of HIT, improved bioavailability, longer half-life requiring less frequent administration, and a more predictable dose response.\(^1,4,27\) The longer half-life of LMWH may also be considered a disadvantage, as it may become troublesome at the time of delivery when rapid cessation of anticoagulant effect is desired.\(^1,4\) However, patients can be transitioned from LMWH to UFH prior to delivery. Another potential disadvantage of LMWH is the higher drug acquisition cost.\(^4\)

### Prophylaxis

When determining the appropriateness of prophylaxis during pregnancy for those with a prior VTE, guidelines suggest

<table>
<thead>
<tr>
<th>Management type</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic LMWH</td>
<td>Enoxaparin 40 mg SC once daily</td>
</tr>
<tr>
<td></td>
<td>Dalteparin 5000 units SC once daily</td>
</tr>
<tr>
<td>Intermediate-dose LMWH(^a)</td>
<td>Enoxaparin 40 mg SC every 12 hours</td>
</tr>
<tr>
<td>Therapeutic LMWH(^b) (adjusted dose, weight-based dose, full dose)</td>
<td>Dalteparin 5000 units SC every 12 hours</td>
</tr>
<tr>
<td>Minidose prophylactic UFH</td>
<td>Dalteparin 100 units/kg every 12 hours</td>
</tr>
<tr>
<td>Prophylactic UFH</td>
<td>Dalteparin 200 units/kg once daily</td>
</tr>
<tr>
<td>Intermediate UFH(^c)</td>
<td>Tinzaparin 175 units/kg once daily(^d)</td>
</tr>
<tr>
<td>Therapeutic UFH (adjusted dose, weight-based dose, full dose)</td>
<td>UFH 5000 units SC every 12 hours</td>
</tr>
<tr>
<td>Postpartum anticoagulation</td>
<td>UFH 7500-10 000 units SC every 12 hours</td>
</tr>
</tbody>
</table>

**Abbreviations:** aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; SC, subcutaneously.

\(^{a}\) As recommended by the Chest 2012 guidelines only.\(^{27}\)

\(^{b}\) May target anti-Xa level of 0.6 to 1.0 units/mL for twice daily regimen.

\(^{c}\) The reader should note that tinzaparin is no longer available on the US market.

\(^{d}\) Unless aPTT is elevated.

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Table 3. Recommended Anticoagulation Regimens During Pregnancy.\(^2,27,44\)
### Table 4. Recommended Thromboprophylaxis Management During Pregnancy.2,27

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Antepartum treatment</th>
<th>Postpartum treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute VTE</td>
<td>Therapeutic LMWH/UFH</td>
<td>Anticoagulation continued for 6 weeks</td>
<td></td>
</tr>
<tr>
<td>Low-risk thrombophilia, no previous VTE</td>
<td>Surveillance only</td>
<td>Postpartum anticoagulation if additional risk factors</td>
<td></td>
</tr>
<tr>
<td>Low-risk thrombophilia, single previous VTE, not on long-term therapy</td>
<td>Prophylactic LMWH/UFH  Intermediate-dose LMWH/UFH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk thrombophilia, no previous VTE, family history VTE</td>
<td>Intermediate LMWH</td>
<td>Postpartum anticoagulation</td>
<td></td>
</tr>
<tr>
<td>High-risk thrombophilia, no previous VTE, no family history VTE</td>
<td>Surveillance only$^b$</td>
<td>Intermediate LMWH</td>
<td></td>
</tr>
<tr>
<td>High-risk thrombophilia, single previous VTE, no long-term anticoagulation</td>
<td>Prophylactic LMWH/UFH  Intermediate LMWH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous single VTE, transient risk factor no longer present$^{c,d}$</td>
<td>Surveillance only</td>
<td>Postpartum anticoagulation</td>
<td></td>
</tr>
<tr>
<td>Previous single VTE, pregnancy- or estrogen-related risk factor</td>
<td>Prophylactic LMWH/UFH  Intermediate LMWH $^b$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous single VTE, idiopathic, not on long-term therapy</td>
<td>Prophylactic LMWH/UFH  Intermediate LMWH $^b$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq$ 2 episodes VTE, not on long-term therapy</td>
<td>Therapeutic LMWH/UFH  Intermediate LMWH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq$ 2 episodes VTE, on long-term therapy</td>
<td>Therapeutic LMWH/UFH  Intermediate LMWH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory and clinical criteria for APS$^b$</td>
<td>Intermediate LMWH/UFH  Prophylactic LMWH $+$ ASA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APLA, antiphospholipid antibody; ASA, aspirin; INR, international normalized ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

$^a$ Postpartum anticoagulation should be greater or equal to antepartum treatment$^2$; includes vitamin K antagonist with a target INR 2 to 3 or prophylactic anticoagulant for 4 to 6 weeks.$^27$

$^b$ Recommended by Chest, 2012$^{27}$ only.

$^c$ Per ACOG$^2$: first degree relative to history of VTE before age 50, obesity, immobility, and other thrombotic risk factors.

$^d$ Does not include pregnancy- or estrogen-related risk factor.

$^e$ Per Chest, 2012$^{27}$: low risk of recurrence.

Patients at low risk of recurrence undergo clinical vigilance during the antepartum period, while those at moderate to high risk of recurrence receive antepartum prophylaxis with prophylactic or intermediate dosages of LMWH or UFH, with preference given to LMWH.2,27 Low risk includes women with a single episode of VTE associated with a transient risk factor, not including pregnancy, or use of estrogen. Moderate to high risk includes women with a history of an idiopathic VTE, pregnancy- or estrogen-related VTE, or multiple prior VTE not currently receiving anticoagulation therapy.2,27 All women with a prior VTE should receive postpartum anticoagulation for 6 weeks with LMWH or vitamin K antagonists (Table 4).2,27

Although the presence of an underlying thrombophilia may increase the risk of pregnancy-related thrombosis, prophylaxis during pregnancy may not be necessary with all thrombophilia. The need for prophylaxis depends on several factors, such as the risk of thrombosis associated with the thrombophilia, the history of previous VTE, family history of VTE, and if the previous VTE was due to a transient risk factor or an idiopathic event. Patients homozygous for FVL or prothrombin 20210A mutation with a positive family history but no prior history of VTE should receive antepartum and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH or UFH, again with preference given to LMWH.2,27 Patients homozygous for FVL or prothrombin 20210A mutation without a previous VTE and no family history, antepartum clinical vigilance and postpartum prophylaxis are recommended.27 For pregnant women with other thrombophilia and a positive family history of VTE, postpartum prophylaxis is suggested, while those without a positive family history may simply undergo clinical vigilance.27 Warfarin may be utilized for postpartum prophylaxis in all patients other than those with protein C or S deficiency due to concerns with warfarin-induced skin necrosis27 (see Table 4). Antiphospholipid syndrome (APS) requires a different approach and is discussed subsequently.

**APS**

APS is a thrombophilia that warrants discussion regarding management in pregnancy. Women with APS who become
pregnancy loss and decrease the risk of thrombosis to the pregnancy loss by 54%. In patients with APS without a history of thrombosis, combination therapy with LMWH, adjusted-dose LMWH or 75% of a therapeutic dose of LMWH during pregnancy, followed by initiation of oral anticoagulants postpartum. In these patients, American College of Chest Physicians recommend adjusted-dose LMWH or 75% of a therapeutic dose of LMWH during pregnancy, followed by initiation of oral anticoagulants postpartum. Refer to Table 3 for recommended anticoagulation regimens during pregnancy.

For women with APS who have a history of a single episode of thrombosis but are not being treated with anticoagulants indefinitely, antepartum prophylactic or intermediate-dose LMWH or UFH in addition to postpartum prophylaxis is recommended.

Postpartum Management in APS

In patients previously treated with warfarin for a history of thrombosis, postpartum anticoagulation with UFH or LMWH overlapped with warfarin therapy until a target international normalized ratio (INR) of 2.0-3.0 is obtained is recommended. Table 4 includes recommended postpartum treatment options according to clinical setting. Postpartum prophylaxis is recommended in those with a history of a single episode of thrombosis, not being treated with anticoagulants postpartum.

For women who have not experienced a previous thrombotic episode, the risk of thrombosis is unclear in patients with APS; therefore, guidance for postpartum management is limited. According to Giannakopoulos and Krulis, therapy should be individualized based on patient-specific risk factors (ie, APLA positivity on multiple instances, age > 35, family history, immobility, obesity, and cesarean section). Clinical observation is suggested in women with other thrombophilias, (w/ exception of Factor V leiden and prothrombin 20210 A mutation) without a family history of VTE and no previous thrombosis. However, studies have not shown improved neonatal outcomes when compared with UFH and aspirin. Prednisone has also been proposed as a potential treatment modality in combination with aspirin but is associated with more preeclampsia and adverse effects.

APS With a History of Thrombosis

Since patients with APS are at a high risk of recurrent thrombosis, patients are often treated with warfarin indefinitely. Due to teratogenicity associated with warfarin therapy, warfarin should be discontinued and therapeutic anticoagulation with UFH or LMWH is suggested during pregnancy. In these patients, American College of Chest Physicians recommend adjusted-dose LMWH or 75% of a therapeutic dose of LMWH during pregnancy, followed by initiation of oral anticoagulants postpartum. Refer to Table 3 for recommended anticoagulation regimens during pregnancy.

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Emerging Concepts

Assisted Reproductive Technology

Assisted reproductive technology (ART) may be associated with an increased risk of thrombosis. Population prevalence studies have demonstrated an overall thrombosis estimate of
2.66 per 1000 cycles, compared to 0.97 for natural pregnancy.\textsuperscript{66,67} Thrombosis occurred in 0.1\% (95\% CI 0\%-0.3\%) to 0.3\% (95\% CI 0\%-0.8\%) of cycles in large retrospective cohort studies.\textsuperscript{68,69} Thrombotic risk with ART is significantly higher in the first trimester but does not differ in the second or third trimester.\textsuperscript{57,70} The overall magnitude of VTE risk in patients undergoing ovarian stimulation is low, but it does represent a 10-fold increase in the baseline relative risk in women of reproductive age.\textsuperscript{21}

**Ovarian Hyperstimulation Syndrome**

The incidence of thrombosis may be higher in women with ovarian hyperstimulation syndrome (OHSS), with a reported incidence of 4.1\% (95\% CI 1.1\%-13.7\%) in severe cases.\textsuperscript{70} OHSS was reported in 90\% of arterial events and 78\% of venous events; additionally, 98\% of reported thrombosis occurred after ovulation induction.\textsuperscript{71} Arterial events occurred earlier after embryo transfer (10.7 days) than venous events (42.4 days) and were almost always concurrent with the development of OHSS, whereas venous events occurred after the resolution of OHSS.\textsuperscript{71}

During ovarian stimulation, there is an increase in the levels of estradiol, vWF, factors V and VIII, and fibrinogen, as well as an increase in activated protein C resistance in addition to a reduction in antithrombin levels and proteins C and S.\textsuperscript{71} Both arterial and venous thrombotic events have been reported. Venous thrombosis in relation to ART has been reported in unusual locations, such as the upper extremities, head, and neck, compared to the usual location in the left leg. Ischemic stroke has been reported as the most common arterial event.\textsuperscript{71} The occurrence of thrombotic events in the neck and upper extremities may be due to estrogen-rich lymphocytic drainage from ascitic fluid into the thoracic duct, which further drains into the left subclavian vein, or obstruction at the base of the subclavian and jugular veins due to brachial cysts that fill with fluid during OHSS.\textsuperscript{71}

Dosage and duration of thromboprophylaxis have not been well studied to date. However, due to the increase in thrombotic events associated with OHSS, prophylaxis with LMWH may be considered. Recent guidelines recommend that patients who develop severe OHSS receive prophylactic doses of LMWH for 3 months after resolution of OHSS.\textsuperscript{27} Other suggestions include initiating thromboprophylaxis and continuing for a minimum duration of 4 to 8 weeks beyond the resolution of OHSS or until the end of the first trimester in women who conceive.\textsuperscript{71,72} In women who develop thrombosis, therapeutic doses of LMWH or UFH should be initiated and continued as recommended by practice guidelines.\textsuperscript{2,27,71}

**Repeated Implantation Failure**

Acquired and inherited thrombophilia have been implicated in women with repeated implantation failure after ART.\textsuperscript{72} Factor V Leiden homozygosity, prothrombin mutation homozygosity, and APS are thrombophilia associated with the highest risk of VTE in pregnancy, along with pregnant women who have a family history of thromboembolism.\textsuperscript{2,28,77} Warfarin should be avoided during pregnancy due to the risk of teratogenicity. Treatment with LMWH or UFH is recommended for acute VTE, with preference often given to LMWH due to ease of dosing and other advantages over UFH.\textsuperscript{5,10,28} Prophylactic or treatment doses of

Studies of LMWH use in women with repeated implantation failures have demonstrated conflicting but encouraging results. Qublan et al found that LMWH use was associated with an increase in implantation rates (20.9\% vs 6.1\%, $P < .001$), pregnancy rates (31\% vs 9.6\%, $P < .05$), and live birth rate (23.8 vs 2.8, $P < .05$) compared to placebo.\textsuperscript{74} In a study of 150 women with 2 or more failed ART cycles, LMWH use was found to correlate with an increase in live births (34.7\% vs 26.7\%, 95\% CI $-4.2\%$-$24.9\%$; $P = .29$).\textsuperscript{75} Although not statistically significant, the 30\% relative increase in live births calls for additional research on empirical use of LMWH in women with repeated implantation failures.\textsuperscript{76}
LMWH or UFH may be warranted during pregnancy and/or the postpartum period in women with prior VTE and in certain women with underlying thrombophilia.

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