Venous thromboembolism (VTE) is a major cause of maternal morbidity and mortality. The estimated incidence of VTE during pregnancy and the postpartum period is 1–2 per 1000 deliveries. The risk of VTE is particularly elevated during the postpartum period and especially after cesarean delivery. There is considerable variation in the approach to prophylaxis of VTE in pregnancy, including after cesarean delivery. Current guidelines by various professional organizations provide conflicting recommendations based on low-grade evidence, mainly from observational data. This Consult discusses the different guidelines on prophylaxis of VTE after cesarean delivery and provides recommendations based on the available evidence.

**What are the current guidelines for venous thromboembolism prophylaxis after cesarean delivery?**

The American College of Obstetricians and Gynecologists (ACOG) currently recommends that all women undergoing a cesarean delivery receive mechanical prophylaxis using pneumatic sequential compression devices started preoperatively and continued until the woman is ambulatory. The
The guideline also recommends that all women be screened for risk factors for VTE. For women with additional risk factors, individual risk assessment may support the use of combined pharmacologic and mechanical prophylaxis. Furthermore, ACOG recommends that if such risk factors persist during the postpartum period, pharmacologic prophylaxis for up to 6 weeks should be considered. Several guidelines are available that define risk factors for VTE, including those from the American College of Chest Physicians (ACCP), Royal College of Obstetricians and Gynaecologists (RCOG), and National Partnership for Maternal Safety (NPMS). ACOG does not endorse any specific guideline because of the lack of available evidence but encourages hospitals to evaluate women for risk factors for VTE and to implement a prophylaxis protocol weighing benefits, harms, and cost-effectiveness.

The risk threshold at which pharmacologic prophylaxis of VTE is warranted remains unknown. By extrapolating from evidence in patients who have undergone general surgery, the ACCP suggests that the benefits of thromboprophylaxis outweigh potential harm when the absolute risk of VTE is 3% or higher.4 The ACCP categorizes risk factors as major (odds ratio [OR] >6) or minor (OR >6 when combined). The presence of 1 major risk factor, 1 minor risk factor in the setting of an emergent cesarean delivery, or 2 or more minor risk factors suggests a VTE risk above 3%.4 For women undergoing cesarean delivery with no risk factors for VTE, the ACCP recommends no prophylaxis other than early mobilization.4 For women at very high risk for VTE, combined prophylaxis (pharmacologic and mechanical) is suggested. If risk factors persist after delivery, prophylaxis is suggested for up to 6 weeks postdelivery. The ACCP risk stratification model is summarized in Table 1.

RCOG recommends that “all women who have had caesarean [sic] sections should be considered for thromboprophylaxis with low-molecular-weight heparin (LMWH) for 10 days after delivery apart from those having an elective caesarean section who should be considered for thromboprophylaxis with LMWH for 10 days after delivery if they have any additional risk factors.”5 This guideline recommends prophylaxis with LMWH for 10 days after delivery in women at intermediate risk for VTE and for at least 6 weeks after delivery in women at high risk for VTE. In these guidelines, an intrapartum or urgent cesarean delivery meets the criteria for intermediate risk. Other risk factors must be present for women to be considered at high risk for VTE. The RCOG risk stratification model is summarized in Table 1.

The NPMS recommends a consensus bundle for the prevention of VTE during pregnancy and the puerperium.6 For all women undergoing cesarean deliveries, the NPMS recommends the use of universal pneumatic compression devices. The addition of pharmacologic prophylaxis may be considered for women at high risk for VTE based on the use of either the RCOG guidelines or the modified Caprini scoring system. Furthermore, the NPMS bundle states that “given the challenges in consistently identifying women with risk factors,” hospitals may consider providing pharmacologic VTE prophylaxis to all women undergoing a cesarean delivery.

Is there sufficient evidence to recommend one specific guideline over the other?

For certain subgroups of women, recommendations from available guidelines are consistent. In general, all women with a previous episode of VTE require prophylactic doses of LMWH or unfractionated heparin (UFH) for at least 6 weeks after delivery.3–5 Similarly, women with no previous personal history of VTE but who have tested positive for one of the high-risk inherited thrombophilias (antithrombin III deficiency, homozygous Factor V Leiden or G20210A, or heterozygous for both Factor V Leiden and G20210A) should also receive pharmacologic VTE prophylaxis after cesarean delivery.3–5 For women with no previous VTE who have a low-risk thrombophilia, postpartum pharmacologic prophylaxis is warranted because a cesarean delivery is an additional risk factor for VTE among this subgroup of women.3–5 Women with a previous diagnosis of antiphospholipid antibody syndrome should receive prophylactic or therapeutic doses of heparin (depending on previous history of VTE) during the puerperium irrespective of mode of delivery.

The main discrepancy among current guidelines concerns pharmacologic prophylaxis for women with no history of VTE and no inherited or acquired thrombophilia. A 2016 study of 293 patients who underwent cesarean delivery at a single tertiary center in the United States found that if recommendations from RCOG were followed, 85.0% (95% confidence interval [CI], 80.5%–88.6%) of women undergoing cesarean deliveries would be candidates for postpartum pharmacologic VTE prophylaxis, compared with 1.0% (95% CI, 0.3%–3.0%) under ACOG guidelines and 34.8% (95% CI, 29.6%–40.4%) under ACCP guidelines.7

Recommendations from different organizations are currently based on observational studies and expert opinions because clinical trials are lacking.8 The risk-benefit ratio of pharmacologic prophylaxis after cesarean delivery depends on the accurate determination of the true incidence of VTE. Administrative and retrospective data obtained from analysis of large databases may overestimate the incidence of VTE (up to 4% among women at high risk for VTE), resulting in a similar overestimation of the benefit of any intervention aimed at preventing it.9 The latter is particularly important when considering the ACCP guidelines, in which recommendations are based on a VTE risk of 3% or greater, when in reality the incidence after cesarean delivery is significantly lower.9 In prospective studies, although not designed specifically to evaluate the incidence of VTE, clinical VTE after cesarean delivery was noted in 0.6 per 1000 deliveries for elective cesarean delivery and 0.8 per 1000 deliveries after emergent cesarean delivery.10

Based on observational data, some authors have attempted to calculate the number needed to treat (NNT) to prevent 1 episode of VTE during the postpartum period.

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**Table 1**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>ACCP Categorization</th>
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</thead>
<tbody>
<tr>
<td>Major</td>
<td>OR &gt;6</td>
</tr>
<tr>
<td>Minor</td>
<td>OR &gt;6 when combined</td>
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</table>

**ACCP Risk Stratification Model**

- **Intermediate Risk**: 1 major risk factor or 2 or more minor risk factors.
- **High Risk**: Any clinical VTE after cesarean delivery was noted in 0.6 per 1000 deliveries for elective cesarean delivery and 0.8 per 1000 deliveries after emergent cesarean delivery.10
Sultan et al\textsuperscript{11} reported that among women deemed at high risk for VTE postpartum, 640 would require prophylaxis to prevent 1 episode of VTE. Other authors have reported an NNT as high as 4000 among women at high risk for VTE who underwent cesarean delivery.\textsuperscript{9}

The potential benefit of pharmacologic prophylaxis needs to be weighed against the potential for adverse outcomes associated with the intervention. The use of pharmacologic VTE prophylaxis after cesarean delivery has been associated with increased rates of wound separation and wound hematomas.\textsuperscript{8,11–13} The number needed to harm (NNH) with the use of pharmacologic VTE prophylaxis after cesarean delivery has been reported to be as low as 200.\textsuperscript{9} In the absence of adequately powered clinical trials, accurate calculations of the NNT and NNH are limited. However, the available evidence suggests that the NNH may be lower than the NNT in most scenarios, particularly in the absence of risk factors or the presence of a minor risk factor.

### TABLE 1

<table>
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<tr>
<th>Organization</th>
<th>Recommendation</th>
<th>Risk stratification</th>
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</table>
| American College of Obstetricians and Gynecologists\textsuperscript{3} | - Pneumatic compression devices for all women undergoing cesarean delivery  
- Women with additional risk factors for VTE may benefit from pharmacologic prophylaxis. | A preferred risk scoring system is not endorsed; recommends each facility carefully consider the risk assessment protocols available and implement one in a systematic way to reduce the incidence of VTE in pregnancy and the postpartum period. |
| American College of Chest Physicians\textsuperscript{4} | - Other than early mobilization, no prophylaxis is recommended in women without risk factors.  
- Prophylaxis with LMWH is suggested when 1 major or 2 or more minor risk factors are present or when 1 minor risk factor is present in the setting of emergent cesarean delivery.  
- In women at very high risk for VTE, combined pharmacologic and mechanical prophylaxis is suggested.  
- If risk factors persist after delivery, prophylaxis is suggested for up to 6 weeks postpartum. | Major risk factors are as follows:  
- Immobility for at least 1 week antepartum  
- Postpartum hemorrhage with surgery  
- Previous VTE  
- Preeclampsia with fetal growth restriction  
- Antithrombin deficiency  
- Factor V Leiden or G20210A mutations  
- Blood transfusion  
- Postpartum infection  
- Systemic lupus erythematosus  
- Heart disease  
- Sickle cell disease  
Minor risk factors are as follows:  
- Obesity  
- Multiple pregnancy  
- Postpartum hemorrhage  
- Smoking  
- Fetal growth restriction  
- Preeclampsia  
- Protein C or S deficiency |
| Royal College of Obstetricians and Gynaecologists\textsuperscript{5} | Women at high risk for VTE should receive LMWH for 6 weeks after delivery; women at intermediate risk for VTE should receive LMWH for at least 10 days after delivery. For women at low risk for VTE, early mobilization and avoidance of dehydration are recommended. | High-risk patients  
Any previous VTE, any woman requiring antenatal LMWH, high-risk thrombophilia, low-risk thrombophilia with family history of thrombosis  
Intermediate-risk patients  
Any one of the following:  
- Cesarean delivery during labor, BMI >40 kg/m\textsuperscript{2}, postdelivery readmission, surgical procedures during the puerperium, cancer, heart failure, active lupus, nephrotic syndrome, sickle cell disease, type 1 diabetes with nephropathy, inflammatory bowel disease, intravenous drug use  
or  
Two or more of the following:  
- Age >35 years, parity >3, obesity, smoker, elective cesarean delivery, family history of VTE, low-risk thrombophilia, varicose veins, current systemic infection, preeclampsia, immobility, multiple pregnancy, preterm delivery, stillbirth, operative vaginal delivery, prolonged labor >24 hours, postpartum hemorrhage |

\textsuperscript{6}BMI, body mass index; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

Another consideration in making recommendations is that the use of risk assessment models (eg, Caprini and Padua) to predict VTE after cesarean delivery has not been adequately studied. The authors of a 2018 study questioning the utility of risk assessment models during the peripartum period suggested the establishment of a maternal clinical registry and more extensive research to identify optimal models with which to predict VTE risk in the obstetrical population.14

At present, the available evidence suggesting that universal (or near universal) pharmacologic VTE prophylaxis effectively reduces maternal mortality is limited.8 After the implementation of prophylactic guidelines in the United Kingdom, a decrease in maternal mortality secondary to VTE was noted between 2004 and 2008. However, more recent analyses found that the reduction has not been sustained, with an increase in VTE-related maternal mortality after 2009 when compared with the initial reduction noticed in previous years.15 In particular, the available data do not allow us to attribute any reduction in mortality specifically to prophylaxis after cesarean delivery because the RCOG recommendations would have increased the use of thromboprophylaxis in a number of different clinical scenarios (eg, use of prophyaxis in the antepartum period or after vaginal deliveries among women with risk factors for VTE). Any attributable benefit of universal pharmacologic VTE prophylaxis after cesarean delivery on maternal mortality will likely be low because of the rarity of the event. A recent study reported only 1 maternal death from VTE among 465,880 women undergoing a cesarean delivery who received mechanical prophylaxis (eg, sequential compression devices).16

We recommend that all women who undergo cesarean delivery receive sequential compression devices starting before surgery and that the compression devices be used continuously until the patient is fully ambulatory. (GRADE 1C)

We suggest that women with a previous personal history of deep venous thrombosis or pulmonary embolism who undergo cesarean delivery receive both mechanical (starting preoperatively and continuing until ambulatory) and pharmacologic (for 6 weeks postoperatively) prophylaxis. (GRADE 2C)

We suggest that women with a personal history of an inherited thrombophilia (high-risk or low-risk) but no previous thrombosis who undergo cesarean delivery receive both mechanical (starting preoperatively and continuing until ambulatory) and pharmacologic (for 6 weeks postoperatively) prophylaxis. (GRADE 2C)

Which pharmacologic agents are commonly used for prophylaxis of venous thromboembolism?

The 2 most common agents used for prophylaxis of VTE are LMWH and UFH. Current guidelines recommend LMWH (eg, enoxaparin) as the first-line pharmacologic agent.3,4 Enoxaparin has a half-life of 4 to 6 hours and is eliminated by the kidney. Therefore, it is not recommended in patients with significant renal dysfunction, defined as creatinine clearance of less than 30 mL/min.17 Compared with UFH,
<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Clarity of risk and benefit</th>
<th>Quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A. Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risks and burdens or vice versa.</td>
<td>Consistent evidence from well-performed, randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.</td>
<td>Strong recommendation that can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.</td>
</tr>
<tr>
<td>1B. Strong recommendation, moderate-quality evidence</td>
<td>Benefits clearly outweigh risks and burdens or vice versa.</td>
<td>Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.</td>
<td>Strong recommendation that applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.</td>
</tr>
<tr>
<td>1C. Strong recommendation, low-quality evidence</td>
<td>Benefits seem to outweigh risks and burdens or vice versa.</td>
<td>Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.</td>
<td>Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.</td>
</tr>
<tr>
<td>2A. Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced with risks and burdens.</td>
<td>Consistent evidence from well-performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change confidence in the estimate of benefit and risk.</td>
<td>Weak recommendation; best action may differ depending on circumstances or patients or societal values.</td>
</tr>
<tr>
<td>2B. Weak recommendation, moderate-quality evidence</td>
<td>Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks, and burdens.</td>
<td>Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an effect on confidence in the estimate of benefit and risk and may change the estimate.</td>
<td>Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.</td>
</tr>
<tr>
<td>2C. Weak recommendation, low-quality evidence</td>
<td>Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens.</td>
<td>Evidence from observational studies, unsystematic clinical experience, or randomized controlled trials with serious flaws. Any estimate of effect is uncertain.</td>
<td>Very weak recommendation; other alternatives may be equally reasonable.</td>
</tr>
<tr>
<td>Best practice</td>
<td>Recommendation in which either (1) there is an enormous amount of indirect evidence that clearly justifies strong recommendation (direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize) or (2) recommendation to the contrary would be unethical.</td>
<td>—</td>
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Adapted from Guyatt et al.22

enoxaparin has the advantage of better bioavailability, longer half-life, more predictable anticoagulation effect, less bleeding risks, and less risk of heparin-induced thrombocytopenia and osteopenia.\textsuperscript{17} \textbf{We recommend the use of LMWH as the preferred thromboprophylactic agent in pregnancy and the postpartum period (GRADE 1C).}

For purposes of prophylaxis, the recommended dose of enoxaparin is typically 40 mg subcutaneously once a day. Obese women may require higher doses; however, the optimal dose is unknown. Some evidence supports the use of intermediate doses of enoxaparin (40 mg subcutaneously every 12 hours) for obese women.\textsuperscript{18} Other studies suggest that compared with a fixed-dose regimen (eg, 40 mg subcutaneously every 12 hours), a weight-based prophylactic dose of 0.5 mg/kg subcutaneously every 12 hours of enoxaparin in morbidly obese women after cesarean delivery results in anti-Xa levels that are more often within the desired prophylactic target range.\textsuperscript{19} It is unknown if the latter strategy results in fewer thrombotic events.

When pharmacologic thromboprophylaxis is needed in pregnant women with class III obesity, we suggest the use of intermediate doses of enoxaparin (GRADE 2C).

UFH has a shorter half-life than LMWH of 60 to 90 minutes and is mostly cleared by the reticuloendothelial system, rendering it a good choice in women with renal disease.\textsuperscript{17} Recommended prophylactic dosages range from 5000 to 10,000 units subcutaneously every 12 hours depending on gestational age (5000 units subcutaneously every 12 hours in the first trimester, 7500 units subcutaneously every 12 hours in the second trimester, and 10,000 units subcutaneously every 12 hours during the third trimester).\textsuperscript{3} In the postpartum period, doses of 5000 units subcutaneously every 8 to 12 hours are commonly used. There are insufficient data to recommend the use of new oral anticoagulants (eg, apixaban, rivaroxaban, dabigatran) during the postpartum period.

\textbf{When is the optimal time to start thromboembolism prophylaxis after a cesarean delivery?}

Current ACOG guidelines recommend starting mechanical prophylaxis of VTE with sequential compression devices preoperatively in all women undergoing cesarean delivery.\textsuperscript{3} Recent guidelines have addressed the optimal interval between neuraxial anesthesia and initiation of pharmacologic VTE prophylaxis to prevent the development of spinal or epidural hematomas.\textsuperscript{20} For LMWH, these recommendations consider both the time when the neuraxial block was performed preoperatively and the time when the catheter was removed postoperatively. Prophylactic doses of enoxaparin (40 mg subcutaneously every day) may be started postoperatively as early as 4 hours after catheter removal \textbf{but not earlier than} 12 hours after the block was performed. Intermediate doses of enoxaparin (40 mg subcutaneously every 12 hours) and therapeutic doses may also be started as early as 4 hours after catheter removal but not earlier than 24 hours after the block was performed. Prophylactic doses of UFH may be started as early as 1 hour after removal of the neuraxial catheter.\textsuperscript{20}

In addition to concerns about spinal hematomas, the risk of postoperative bleeding should also be considered in the timing to start prophylaxis of VTE. With prophylactic doses of anticoagulation, bleeding complications are usually mild, such as wound hematomas, and rarely result in life-threatening hemorrhage (unlike bleeding risks with the use of full-dose anticoagulation in the postoperative period).\textsuperscript{12} In cases with significant intraoperative bleeding complications, the decision of when to start pharmacologic prophylaxis (if indicated) must be individualized while recognizing that postpartum hemorrhage, blood transfusion, and prolonged surgery are risk factors for VTE. In these cases, initiation of UFH, which is reversible and has a shorter half-life, may be prudent.

\textbf{Conclusions}

VTE remains an important cause of maternal morbidity and mortality during pregnancy and the postpartum period. The use of mechanical prophylaxis sequential compression devices is an inexpensive, safe intervention and should be used in all women undergoing cesarean delivery until the woman is fully ambulatory. The decision to add pharmacologic prophylaxis depends on the presence or absence of certain risk factors. Women with a previous personal history of deep venous thrombosis or pulmonary embolism and women with a personal history of an inherited thrombophilia (either high-risk or low-risk) should receive pharmacologic prophylaxis after cesarean delivery. The use of universal or near-universal pharmacological prophylaxis for women undergoing cesarean delivery, other than those with a previous thrombosis or an inherited thrombophilia, cannot be recommended until further studies demonstrate that such a strategy is beneficial. At present, the available VTE risk stratification tools used to decide for or against pharmacologic prophylaxis have not been validated in women undergoing cesarean delivery. Individualization of care is recommended for women at very high risk for VTE. \textbf{We recommend that each institution develop a patient safety bundle with an institutional protocol for VTE prophylaxis among women who undergo cesarean delivery (Best Practice).}

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Kotas A. Postpartum venous thromboembolism prophylaxis may cause more harm than benefit: a critical analysis of international guidelines through an evidence-based lens. BJOG 2018;125:1109–16.


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