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Prevention of Venous Thromboembolism in Gynecologic Surgery

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are collectively referred to as "venous thromboembolic events" (VTE). Despite advances in prophylaxis, diagnosis, and treatment, VTE remains a leading cause of cost, disability, and death in postoperative and hospitalized patients (1, 2). Beyond the acute sequelae of leg pain, edema, and respiratory distress, VTE may result in chronic conditions, including postthrombotic syndrome (3), venous insufficiency, and pulmonary hypertension. This Practice Bulletin has been revised to reflect updated literature on the prevention of VTE in patients undergoing gynecologic surgery and the current surgical thromboprophylaxis guidelines from the American College of Chest Physicians (4). Discussion of gynecologic surgery and chronic antithrombotic therapy is beyond the scope of this document.

Background

Epidemiology

Rates of VTE after gynecologic surgery for benign indications are similar to those reported in the general surgery literature and range from 15% to 40% in the absence of thromboprophylaxis (4, 5). Although most cases of postoperative VTE begin within 24–72 hours after surgery (6), it often is not clinically apparent until 6–15 days later (7, 8). The risk of VTE may persist beyond 4 weeks after gynecologic surgery in the highest risk patients, such as those undergoing cytoreductive surgery for ovarian cancer (9). Most patients who die from PE succumb within 30 minutes of developing symptoms, leaving little time for therapeutic interventions (10). Thus, clinicians should focus on identifying at-risk patients and instituting consistent, effective thromboprophylaxis to reduce the incidence of this frequent and often preventable cause of death.

Risk Factors

Numerous environmental, inherited, and acquired risk factors influence coagulation (Box 1). Most inherited factors do not result in VTE until the onset of a precipitating event, such as pregnancy, surgery, or exogenous hormone use (4, 11, 12). Patients undergoing bed rest are at increased risk of developing VTE, but there is no standard for defining immobility, which makes it difficult to assess VTE risk independent of other factors that would render a patient immobile (13, 14). Hospitalization and surgery also are associated with an increased likelihood of thrombosis, with odds ratios (ORs) of 11.1 (95% CI, 4.7–25.9) and 5.9 (95% CI, 3.4–10.1), respectively (12).

Although selective estrogen receptor modulators (SERMs), such as tamoxifen, are associated with an increased risk of VTE (15) (Box 1), there currently are no universally accepted guidelines for the use of SERMs in patients undergoing surgical procedures (16). Most of the available data on perioperative SERM use are from breast reconstruction studies that do not include VTE or PE incidence as a primary outcome (17).

The presence of a thrombophilia in a patient undergoing major surgery also confers an increased risk of VTE and may place a patient into the high-risk category (4). Factor V Leiden mutation and prothrombin gene mutation G20210A are the most common mutations found in patients with VTE (12).

Box 1. Caprini Score to Assess Risk of Venous Thromboembolism

1 point for each of the following:

Age 41–60 years
Minor surgery
BMI greater than 25 kg/m^2
Swollen legs
Varicose veins
Pregnancy or postpartum state
History of unexplained or recurrent pregnancy losses (greater than three)
Oral contraceptive, hormone replacement, or selective estrogen receptor modulator use*
Sepsis (less than 1 month)
Serious lung disease, including pneumonia (less than 1 month)
Abnormal pulmonary function
Acute myocardial infarction
Congestive heart failure (less than 1 month)
History of inflammatory bowel disease
Medical patient on bed rest

2 points for each of the following:

Age 61–74 years
Major open surgery (greater than 45 minutes)
Laparoscopic surgery (greater than 45 minutes)
Malignancy
Confined to bed (greater than 72 hours)
Central venous access

3 points for each of the following:

Age 75 years or older
History of VTE
Family history of VTE
Factor V Leiden
Prothrombin 20210A
Lupus anticoagulant
Anticardiolipin antibodies
Elevated serum homocysteine
Heparin-induced thrombocytopenia
Other congenital or acquired thrombophilia

5 points for each of the following:

Stroke (less than 1 month)
Elective arthroplasty
Hip, pelvis, or leg fracture
Acute spinal cord injury (less than 1 month)

Abbreviations: BMI, body mass index; VTE, venous thromboembolism.

*Cronin M, Dengler N, Krauss ES, Segal A, Wei N, Daly M, et al. Completion of the updated Caprini Risk Assessment Model (2013 version). Clin Appl Thromb Hemost 2019;25:3.

Adapted from Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines [published erratum appears in Chest 2012;141:1369]. Chest 2012;141(suppl 2):e227S–77S.

Thromboprophylaxis

Thromboprophylactic methods can be divided into mechanical and pharmacologic methods. Mechanical methods reduce venous stasis and may promote endogenous fibrinolysis. Pharmacologic methods prevent clot formation by exerting effects at different points in the clotting cascade.

A variety of prophylactic methods effectively will reduce DVT formation. Most studies have not included a sufficient number of participants to show that thromboprophylaxis decreases the risk of PE. However, because DVT in the leg or pelvic veins precedes most fatal cases of PE, it seems reasonable to assume that the prevention of DVT also will result in the reduction of PE.

Clinical Considerations and Recommendations

▶ ***How are venous thromboembolism risk and the need for thromboprophylaxis assessed in the perioperative period?***

Before gynecologic surgery, routine VTE risk assessment should be performed using the Caprini score (4, 18). A complete history and physical examination are necessary to identify VTE risk factors that can be used to determine a Caprini score and classify patients by level of risk (Box 1). Physicians also should explicitly elicit and document a complete medication history including complementary, botanical, or other herbal products. For example, vitamin K antagonists are well known to have interactions with herbs, food, and other drugs that can lead to overanticoagulation and hemorrhage or underanticoagulation and thrombosis (19).

The Caprini score is extensively used and has been validated in plastic surgery patients and general surgery patients (20–22). Before gynecologic surgery, patients should be stratified based on the summed Caprini score into one of three risk categories for VTE: 1) low (1.5%), 2) moderate (3.0%), and 3) high risk (6.0%) (4) (Table 1). The American College of Chest Physicians has defined each of these risk groups by the expected rate of VTE in a population of patients undergoing general, abdominal–pelvic, bariatric, vascular, and plastic surgery without thromboprophylaxis (4).

Table 1. Recommended Thromboprophylaxis by Risk Level

Risk of symptomatic VTE	Caprini score	Risk of major bleeding complications*	
		Average risk (~1%)	High risk (~2%)
Low (~1.5%)	1–2	Mechanical prophylaxis, preferably with IPC	
Moderate (~3.0%)	3–4	LDUH, LMWH, or mechanical prophylaxis, preferably with IPC	Mechanical prophylaxis, preferably with IPC
High (~6.0%)	5 or greater	Pharmacologic prophylaxis (LDUH or LMWH) plus mechanical prophylaxis (preferably with IPC)	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis can be added
High-risk cancer surgery	5 or greater	LDUH *or* LMWH plus mechanical prophylaxis (preferably with IPC) and extended-duration prophylaxis with LMWH postdischarge	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis can be added
High risk, LDUH and LMWH contraindicated or not available	5 or greater	Fondaparinux or low-dose aspirin (160 mg)†; or mechanical prophylaxis, preferably with IPC; or both	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis with fondaparinux can be added

Abbreviations: IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

*Major bleeding complications are defined as complications such as wound hematoma formation and reoperation for postoperative bleeding.

†Low-dose aspirin has been studied only in the orthopedic population and may not be adequate prophylaxis for the gynecologic surgery patient.

Modified from Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines [published erratum appears in Chest 2012;141:1369]. Chest 2012;141(suppl 2):e227S–77S.

Box 2. Risk Factors for Major Bleeding Complications

- Active bleeding
- Acute stroke
- Complex surgery (defined as two or more procedures, difficult dissection, or more than one anastomosis)
- Concomitant use of anticoagulants, antiplatelet therapy, or thrombolytic drugs
- Known, untreated bleeding disorder
- Lumbar puncture, epidural, or spinal anesthesia within previous 4 hours or next 12 hours
- Malignancy
- Previous major bleeding
- Severe renal or hepatic failure
- Thrombocytopenia
- Uncontrolled systemic hypertension

Adapted from Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines [published erratum appears in Chest 2012;141:1369]. Chest 2012;141(suppl 2):e227S–77S.

To determine the appropriate thromboprophylaxis regimen, the risk of VTE is balanced against an individual patient's risk of bleeding complications (Table 1). The list of risk factors in Box 2 can be used as a guide to identify patients who are at increased risk of major bleeding complications. The American College of Chest Physicians calculated the bleeding risk estimates in Table 1 based on pooled baseline risks from control groups included in randomized trials of pharmacologic studies of general and abdominal–pelvic surgery (4). The cost, benefit, risk, and feasibility of each method should be weighed in determining the appropriate thromboprophylaxis for an individual patient.

▶ ***What are the recommended thromboprophylaxis options for gynecologic surgery patients at low risk of venous thromboembolism?***

For gynecologic surgery patients at low risk of VTE (Box 1), mechanical thromboprophylaxis (preferably with intermittent pneumatic compression) is recommended (Table 1). Graduated compression stockings are a reasonable alternative if intermittent pneumatic compression is not available or is not preferred by the patient. Mechanical prophylaxis devices should be placed before initiation of surgery and continued until the patient is fully ambulatory.

Intermittent Pneumatic Compression

Intermittent pneumatic compression devices reduce stasis by regularly compressing the calf or whole leg with an inflatable pneumatic sleeve. When used during and after major gynecologic surgery, the devices are as effective as low-dose unfractionated heparin and low-molecular-weight heparin (LMWH) in reducing DVT incidence (23, 24). Most studies have not included a sample size large enough to demonstrate efficacy in lowering PE incidence or mortality.

The 2012 American College of Chest Physicians' guidelines for the prevention of VTE in nonorthopedic surgical patients indicate a preference for intermittent pneumatic compression over graduated compression stockings because intermittent pneumatic compression has comparable efficacy to pharmacologic prophylaxis, and graduated compression stockings may be associated with an increased risk of skin complications (4, 25). However, an important limitation to the use of intermittent pneumatic compression is low patient acceptance, with a reported 58% adherence rate among postoperative obstetrics and gynecology patients (26).

Graduated Compression Stockings

In addition to early postoperative ambulation and elevating the foot of the bed, use of graduated compression stockings reduces venous stasis by preventing pooling of blood in the calves. A Cochrane review of 19 randomized controlled trials of patients undergoing surgery (including one trial of gynecologic surgery) found that the use of graduated compression stockings with or without another form of thromboprophylaxis was associated with a significantly decreased incidence of DVT (OR, 0.35; 95% CI, 0.28–0.43) (27). Low cost and simplicity are additional advantages of graduated compression stockings. Correct fit is essential because improperly fitted stockings may act as a tourniquet at the knee or mid-thigh, causing an increase in venous stasis (28). In one study, 23% of participants wearing above-knee stockings and 16% of participants wearing below-knee stockings found the stockings uncomfortable and requested their removal (29). An additional concern with graduated compression stockings is an increased risk of skin complications (ie, skin breaks, ulcers, blisters, and skin necrosis), which was reported in a study of the use of thigh-length graduated compression stockings in patients hospitalized after stroke (4, 25).

▶ ***What are the recommended thromboprophylaxis options for gynecologic surgery patients at moderate risk of venous thromboembolism?***

For gynecologic surgery patients who are at moderate risk of VTE (Box 1) and not at increased risk of bleeding

complications (Box 2), mechanical thromboprophylaxis (preferably with intermittent pneumatic compression) or pharmacologic thromboprophylaxis (with low-dose unfractionated heparin or LMWH) is recommended (Table 1) (4). For gynecologic surgery patients who are at moderate risk of VTE (Box 1) and high risk of major bleeding complications (Box 2), mechanical prophylaxis (preferably with intermittent pneumatic compression) is recommended. (4). For discussion of mechanical thromboprophylaxis methods, please see *What are the recommended thromboprophylaxis options for gynecologic surgery patients at low risk of venous thromboembolism?* earlier in this document.

Pharmacologic Prophylaxis

Low-Dose Unfractionated Heparin

Low-dose, or prophylactic dose, unfractionated heparin is the most extensively studied method of thromboprophylaxis. Numerous controlled trials have shown low-dose unfractionated heparin to be effective in preventing DVT when administered subcutaneously starting 2 hours before surgery and continued every 8–12 hours postoperatively (24, 30, 31). It is important to note that the timing of pharmacologic prophylaxis may vary based on the use of regional anesthesia (see *What are the clinical considerations when using low-molecular-weight heparin or low-dose unfractionated heparin in patients undergoing regional anesthesia*? later in this document). Analysis of randomized trial data from mixed surgical populations shows that low-dose unfractionated heparin compared with no prophylaxis is associated with a reduced incidence of fatal PE (OR, 0.53; 95% CI, 0.31–0.91) and nonfatal symptomatic VTE (OR, 0.44; 95% CI, 0.31–0.63) (4).

Advantages of low-dose unfractionated heparin include well-studied efficacy and low cost compared with LMWH (32). Furthermore, low-dose unfractionated heparin is only minimally excreted by kidneys and can be used safely in patients with renal insufficiency (33). Low-dose unfractionated heparin also has a rapid onset of action and can be readily reversed with protamine sulfate. However, a concern with perioperative low-dose unfractionated heparin use is increased intraoperative and postoperative bleeding. Although randomized trial data from mixed surgical populations show that low-dose unfractionated heparin prophylaxis is associated with an increased risk of nonfatal perioperative bleeding complications compared with no intervention (OR, 1.57; 95% CI, 1.32–1.87) (4), the absolute incidence of major bleeding complication is low (24, 31). In a systematic review of 33,813 patients undergoing general surgery, only 1% of patients receiving low-dose unfractionated heparin experienced major bleeding complications that required reoperation compared with 0.7% of patients in the control group (31). The most common complications were injection site bruising (8.3%), wound hematoma (5.5%), drain site bleeding (0.4%), and hematuria (1.6%). A review of data from three randomized controlled trials of benign gynecologic surgery found that compared with placebo or early ambulation, low-dose unfractionated heparin was associated with similar bleeding outcomes, including transfusion rate, wound hematomas, suction volume, and hemoglobin level; however, in one study, low-dose unfractionated heparin was associated with an increased estimated blood loss (approximately 150 mL) (24).

Low-Molecular-Weight Heparin

Low-molecular-weight heparin has comparable efficacy to low-dose unfractionated heparin for the prevention of VTE and is another option for pharmacologic thromboprophylaxis (4, 34). Advantages of LMWH prophylaxis over low-dose unfractionated heparin include less frequent administration because of its greater bioavailability and longer half-life (34, 35) as well as a decreased risk (less than 1%) of heparin-induced thrombocytopenia (36), such that platelet screening is not recommended (37). In addition, LMWH has more antifactor Xa and less antithrombin activity than low-dose unfractionated heparin, which may decrease the risk of major bleeding and wound hematoma formation. Concerns regarding the use of LMWH include its cost; its limited use in patients with renal impairment, who may need a reduced dose or alternative agent (33); and, unlike low-dose unfractionated heparin, its effects cannot be completely reversed by protamine sulfate.

In a meta-analysis of general surgery studies on the use of LMWH thromboprophylaxis, patients randomized to receive LMWH versus placebo had a significant reduction in asymptomatic DVT (n=513; relative risk [RR], 0.28; 95% CI, 0.14–0.54) and symptomatic PE (n=5,456; RR, 0.25; 95% CI, 0.11–0.73) (34). Patients treated with LMWH had an increased risk of bleeding complications compared with those receiving placebo or no treatment, including wound hematoma (n=5,242; RR, 1.88; 95% CI, 1.54–2.28) and major hemorrhage (n=5,456; RR, 2.03; 95% CI, 1.37–3.01). In the same meta-analysis, comparison of thromboprophylaxis with LMWH versus low-dose unfractionated heparin showed a trend toward reduction in the risk of major hemorrhage and wound hematoma in the LMWH group, but the association did not reach statistical significance (34). Evidence is lacking in the gynecology literature regarding timing of initiation of LMWH in the postoperative period. However,

data from studies of elective hip arthroplasty indicate that the peak efficacy of LMWH ranges between 2 hours preoperatively and 6–8 hours postoperatively (38).

Heparin-Induced Thrombocytopenia

Prophylactic use of low-dose unfractionated heparin is associated with an increased risk of heparin-induced thrombocytopenia, with a reported incidence of 1–5% among postoperative patients (37). In comparison, LMWH prophylaxis is associated with less than a 1% risk of heparin-induced thrombocytopenia (36). The pretest clinical scoring system known as the "4Ts" (thrombocytopenia, timing of platelet count fall, thrombosis or other sequelae, other causes for thrombocytopenia) can be used to help predict which patients are at increased risk of heparin-induced thrombocytopenia and would benefit from heparin-induced thrombocytopenia diagnostic testing and treatment (39). The American Society of Hematology Choosing Wisely® recommendations advise against testing or treating for suspected heparin-induced thrombocytopenia in patients with a low pretest probability of heparin-induced thrombocytopenia, as indicated by a 4Ts score of 0–3 (39).

▶ ***What are the recommended thromboprophylaxis options for gynecologic surgery patients at high risk of venous thromboembolism?***

Dual Thromboprophylaxis

For gynecologic surgery patients who are at high risk of VTE (Box 1) and average risk of bleeding complications (Box 2), dual thromboprophylaxis with a combination of mechanical prophylaxis (preferably with intermittent pneumatic compression) and pharmacologic prophylaxis (low-dose unfractionated heparin or LMWH) is recommended (4, 40). For gynecologic surgery patients who are at high risk of both VTE and bleeding complications, mechanical prophylaxis (preferably with intermittent pneumatic compression) is recommended until the risk of bleeding decreases and pharmacologic prophylaxis can be added (4).

The use of a combined approach possesses inherent appeal because it may reduce both hypercoagulability and venous stasis in high-risk patients undergoing surgery. Evidence to support dual thromboprophylaxis for high-risk gynecologic surgery patients comes mainly from the mixed surgery and gynecologic oncology literature. A Cochrane review found that among patients who underwent high-risk general and specialized surgery, the use of combined prophylaxis was associated with a decreased incidence of DVT (2.19%) compared with intermittent pneumatic compression alone (4.10%) (OR, 0.52; 95% CI, 0.33–0.82) (40). Dual prophylaxis also was associated with a decreased incidence of symptomatic PE (1.20%) compared with pharmacologic prophylaxis alone (2.92%) (OR, 0.39; 95% CI, 0.23–0.64) (40). Specific to gynecology, a study that examined VTE before and after the introduction of a dual prophylaxis strategy in gynecologic oncology patients found a decreased risk of VTE among those receiving dual prophylaxis (41). Similarly, an institutional review found that in patients undergoing complex gynecologic surgery, the initiation of a dual prophylaxis strategy in patients with benign diagnoses also resulted in a decreased rate of VTE (42). Furthermore, a decision analysis in high-risk gynecologic oncology patients found that dual prophylaxis with intermittent pneumatic compression devices and LMWH use is cost effective (43).

Extended Duration Prophylaxis

For patients at high risk of VTE who are undergoing cancer surgery, in-hospital dual thromboprophylaxis and extended-duration pharmacologic prophylaxis with LMWH after hospital discharge are recommended. The American College of Chest Physicians recommends the use of extended-duration prophylaxis of 28 days for high-risk patients with cancer who are undergoing abdominal or pelvic surgery by laparotomy (4).

Of patients with cancer who develop a VTE, 40% will do so more than 21 days after surgery (44). A major prospective trial that included 2,373 patients undergoing general, urologic, or gynecology surgery for cancer assessed the incidence of clinically overt VTE occurring up to 30 days after surgery (44). In this study, 81.6% of patients received in-hospital prophylaxis and 30.7% of patients received extended prophylaxis after hospital discharge. Fifty patients (2.1%) were diagnosed with a clinically overt VTE, including isolated DVT in 10 patients (0.40%), nonfatal PE in 21 patients (0.88%), and death attributed to VTE in 19 cases (0.82%). A placebo-controlled trial of high-risk cancer patients showed that LMWH administered for 1 week versus 4 weeks postoperatively resulted in a 60% reduction in VTE with 4 weeks of treatment and no increase in bleeding (45). In addition to decreasing the risk of VTE, prolonged prophylaxis using the LMWH enoxaparin has been found to be cost effective in patients undergoing surgery for ovarian cancer (46).

Fondaparinux

For gynecologic surgery patients at high risk of VTE for whom both LMWH and low-dose unfractionated heparin are contraindicated or not available and who are not at high risk of major bleeding complications, fondaparinux

or mechanical prophylaxis (preferably with intermittent pneumatic compression), or both is recommended (4, 47, 48). For gynecologic surgery patients at high risk of VTE and major bleeding complications, and for whom both LMWH and low-dose unfractionated heparin are contraindicated or not available, mechanical prophylaxis alone (preferably with intermittent pneumatic compression) is recommended until the risk of bleeding diminishes and pharmacologic prophylaxis with fondaparinux can be added. Fondaparinux, an indirect factor Xa inhibitor that is administered subcutaneously, has been studied for VTE prophylaxis in abdominal surgery and patients undergoing orthopedic surgery (47–50). In a randomized trial, fondaparinux was found to have equivalent efficacy compared with LMWH in patients undergoing major abdominal surgery, without an increase in nonfatal major bleeding complications (RR, 1.43; 95% CI, 0.93–2.21) (4, 49). Similarly, a more recent Cochrane review of perioperative thromboprophylaxis in patients with cancer found that fondaparinux and LMWH had comparable effects on mortality, symptomatic DVT, PE, major bleeding, or minor bleeding, although the authors noted that the certainty of the evidence was low (48).

Direct Oral Anticoagulants

Direct oral anticoagulants (also known as novel oral anticoagulants and target-specific oral anticoagulants) are a newer class of anticoagulants that include direct factor Xa inhibitors (eg, rivaroxaban and apixaban) and direct thrombin inhibitors (eg, dabigatran). Unlike traditional anticoagulant agents, direct oral anticoagulant agents have a rapid onset of clinical activity and a rapid rate of clearance when stopped and do not require routine laboratory monitoring (51). They have been found to have equivalent or superior efficacy to LMWH for the prevention of VTE in orthopedic surgery patients (52–54). The use of direct oral anticoagulants has been studied in gynecologic oncology patients for extended-duration prophylaxis. A prospective study of 400 patients randomized to receive apixaban (2.5 mg twice daily for 28 days) or enoxaparin (40 mg daily for 28 days) found no difference in the incidence of clinically significant bleeding events (primary outcome) or in the rate of VTE (secondary outcome) (55). Apixaban also was associated with increased patient satisfaction. On the basis of these results, the Society of Gynecologic Oncology has included apixaban as an option in its clinical practice recommendations for thromboprophylaxis after gynecologic cancer surgery (51). The cost effectiveness of direct oral anticoagulants for this indication has not been studied to date.

▶ *Should patients undergoing minimally invasive gynecologic surgery receive thromboprophylaxis?*

Mechanical thromboprophylaxis (preferably with intermittent pneumatic compression) generally is sufficient for most patients who undergo minimally invasive gynecologic surgery for benign conditions; however, individualized risk assessment should be considered to determine whether additional prophylaxis is indicated based on patient risk factors for VTE. Minimally invasive surgery is independently associated with a decreased incidence of VTE compared with open surgery for benign gynecologic conditions and other open surgical procedures (56–58). However, factors such as age, surgical complexity, body mass index, cancer, and operative time are associated with an increased incidence of VTE among patients undergoing minimally invasive gynecologic surgery (56, 57, 59–61).

In data from the American College of Surgeons National Surgical Quality Improvement Program database, the incidence of VTE for open hysterectomy was higher (0.6%; 81/12,733 patients) than for minimally invasive hysterectomy (0.2%; 73/31,434; $P<.001$) (57). The reported incidence of VTE among patients undergoing minimally invasive gynecologic surgery also is low (less than 1%) in observational cohort studies (59–63). However, many of these studies included patients who received some form of prophylaxis that was likely preferentially given to those at higher risk, which confounds conclusions about the need for thromboprophylaxis in minimally invasive surgery (64). Given the favorable benefit-risk profile for mechanical prophylaxis, it seems reasonable to consider this form of prophylaxis for patients undergoing minimally invasive surgery who have no additional risk factors for VTE. However, for minimally invasive surgical patients at high risk, the use of pharmacologic prophylaxis may be warranted (64).

▶ *Which patients with perioperative venous thromboembolism should be tested for clotting abnormalities?*

Routine thrombophilia testing should not be performed for patients who experience VTE in the perioperative period (65–67). In this setting, assessment of patient risk factors (eg, concurrent hormone exposure) and family history is recommended. For patients with additional risk factors for thrombophilia, VTE, or both, referral to a specialist in thromboembolic disorders should be considered (65). The American Society of Hematology's Choosing Wisely® initiative recommends against routine thrombophilia testing in adult patients with VTE that

occurs in the setting of major transient risk factors such as surgery, trauma, or prolonged immobility (65). This is because thrombophilia testing does not affect treatment decisions for patients without additional risk factors for VTE, and there is harm associated with incorrectly diagnosing a patient with a thrombophilic disorder (65).

▶ ***Should patients discontinue use of estrogen-containing hormonal contraceptives or menopausal hormone therapy before surgery?***

Combined Hormonal Contraceptives

Use of combined hormonal contraceptives is contraindicated in patients undergoing major surgery with anticipated prolonged immobilization. However, if patients are expected to be ambulatory postoperatively, there is no reason to stop combined hormonal contraceptives before surgery (68, 69). Specifically, pregnancy prevention in the perioperative period should be considered if combined hormonal contraceptives are discontinued; progestin-only options and nonhormonal options may be alternatives. The estrogenic component of combined hormonal contraceptives increases hepatic production of serum globulins involved in coagulation (including factor VII, factor X, and fibrinogen) and increases the risk of VTE in users (69). The normalization of clotting factors associated with stopping combined hormonal contraceptives is not observed unless discontinuation happens 4–6 weeks before major surgery (70). Although all combined hormonal contraceptives are associated with an increased risk of VTE, this risk remains half the elevated risk observed in pregnancy (71–73).

There are no data to guide the appropriate timing for restarting combined hormonal contraceptives in the perioperative period. However, based on expert opinion, it is reasonable to wait until the perioperative risk has diminished, and the patient has returned to a near-normal level of physical activity.

Menopausal Hormone Therapy

Decisions regarding perioperative use of menopausal hormone therapy should be individualized based on clinical risk factors and shared patient–physician decision making. Hormone therapy is associated with an increased risk of VTE, although the absolute incidence is low. In the Women's Health Initiative, participants who used estrogen plus progestin therapy showed a doubled risk of VTE from 1.7 to 3.5 events per 1,000 person-years (74). When using estrogen alone, VTE risk remains modestly elevated with a hazard ratio of 1.32 (95% CI, 0.99–1.75) (75). However, it is unclear whether menopausal hormone therapy should be discontinued in the perioperative period, because limited data suggest that perioperative use of menopausal hormone therapy may not increase the overall risk of VTE (76). Given this uncertainty, shared decision making is recommended with consideration of an individual patient's risk factors for VTE against the risk of short-term discontinuation of menopausal hormone therapy.

▶ ***What are the clinical considerations for thromboprophylaxis in gynecologic surgery patients with obesity?***

A weight-adjusted dosage regimen should be considered for pharmacologic thromboprophylaxis in gynecologic surgery patients with obesity. For patients with obesity who receive mechanical thromboprophylaxis, devices should be inspected to ensure proper fit.

Surgical patients with obesity are at increased risk of VTE (Box 1). Although the optimal dose is not well established, data from the bariatric surgery literature suggest that patients with obesity likely benefit from higher doses of prophylactic anticoagulation. A study of bariatric surgery patients found that 40 mg of LMWH twice daily was superior to 30 mg of LMWH twice daily in preventing VTE (0.6% compared with 5.4%, $P<.01$) and was not associated with an increase in bleeding complications (77). A systematic literature review of six studies with a total of 1,858 bariatric surgery patients found a decreased VTE rate among patients who received weight-adjusted dosages (0.54%) compared with those who received standard dosages (2.0%), with a comparable incidence of bleeding (weight-adjusted dosage, 1.6%; standard dosage, 2.3%) (78). In a retrospective cohort study of hospitalized patients with obesity (body mass index 40 or greater and weight greater than 100 kg), a high-dose thromboprophylaxis regimen (LMWH 40 mg twice daily or low-dose unfractionated heparin 7,500 units three times daily) decreased VTE incidence compared with the standard dosage (LMWH 40 mg once daily or low-dose unfractionated heparin 5,000 units two or three times daily) (OR, 0.52; 95% CI, 0.27–1.00) and did not increase bleeding incidence (OR, 0.84; 95% CI, 0.66–1.07) (79).

▶ ***What are the clinical considerations when using low-molecular-weight heparin or low-dose unfractionated heparin in patients undergoing regional anesthesia?***

Low-Molecular-Weight Heparin

Caution should be used in the timing of spinal or epidural anesthesia in patients using LMWH to avoid the

development of a spinal hematoma. A 2013 U.S. Food and Drug Administration safety announcement described 100 cases of epidural or spinal hematomas that occurred after use of LMWH (enoxaparin) in patients undergoing epidural or spinal anesthesia (80). Many of these patients had multiple risk factors, the most common of which included female sex, age 65 years or older, epidural technique, twice-daily versus once-daily LMWH administration, increased risk of hemorrhage, concomitant use of medications that affect hemostasis (eg, antiplatelets, anticoagulants, nonsteroidal anti-inflammatory drugs), and the presence of an indwelling epidural catheter during LMWH administration (80).

The American Society of Regional Anesthesia and Pain Medicine guidelines recommend that LMWH prophylaxis should be administered at least 12 hours before neuraxial catheter placement or removal. After neuraxial catheter removal, subsequent administration of LMWH prophylaxis should be delayed at least 4 hours (81). Note that twice-daily LMWH prophylaxis should not be used in patients with a neuraxial catheter in place because it is associated with an increased risk of spinal or epidural hematoma (81).

Low-Dose Unfractionated Heparin

In contrast to LMWH, the use of low-dose unfractionated heparin in combination with neuraxial anesthesia is not associated with a significantly increased risk of spinal or epidural hematoma (81, 82). However, to minimize interference with low-dose unfractionated heparin's peak interval of anticoagulant activity, the American Society of Regional Anesthesia and Pain Medicine recommends that low-dose unfractionated heparin prophylaxis should be administered 4–6 hours before neuraxial catheter placement or removal. Postoperative low-dose unfractionated heparin prophylaxis can be administered immediately after neuraxial catheter removal (81). Prophylactic low-dose unfractionated heparin can be administered to patients with a neuraxial catheter in place because it is not associated with an increased risk of spinal hematoma (81).

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- For gynecologic surgery patients who are at high risk of VTE and average risk of bleeding complications, dual thromboprophylaxis with a combination of mechanical prophylaxis (preferably with intermittent pneumatic compression) and pharmacologic prophylaxis (low-dose unfractionated heparin or LMWH) is recommended.
- For patients at high risk of VTE who are undergoing cancer surgery, in-hospital dual thromboprophylaxis and extended-duration pharmacologic prophylaxis with LMWH after hospital discharge are recommended.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Before gynecologic surgery, routine VTE risk assessment should be performed using the Caprini score.
- For gynecologic surgery patients at low risk of VTE, mechanical thromboprophylaxis (preferably with intermittent pneumatic compression) is recommended. Graduated compression stockings are a reasonable alternative if intermittent pneumatic compression is not available or is not preferred by the patient.
- For gynecologic surgery patients who are at moderate risk of VTE and not at increased risk of bleeding complications, mechanical thromboprophylaxis (preferably with intermittent pneumatic compression) or pharmacologic thromboprophylaxis (with low-dose unfractionated heparin or LMWH) is recommended.
- For gynecologic surgery patients who are at moderate risk of VTE and high risk of major bleeding complications, mechanical prophylaxis (preferably with intermittent pneumatic compression) is recommended.
- For gynecologic surgery patients who are at high risk of both VTE and bleeding complications, mechanical prophylaxis (preferably with intermittent pneumatic compression) is recommended until the risk of bleeding decreases and pharmacologic prophylaxis can be added.
- For gynecologic surgery patients at high risk of VTE for whom both LMWH and low-dose unfractionated heparin are contraindicated or not available and who are not at high risk of major bleeding complications, fondaparinux, mechanical prophylaxis (preferably with intermittent pneumatic compression), or both is recommended.
- For gynecologic surgery patients at high risk of VTE and major bleeding complications, and for whom both LMWH and low-dose unfractionated heparin are contraindicated or not available, mechanical prophylaxis alone (preferably with intermittent

pneumatic compression) is recommended until the risk of bleeding diminishes and pharmacologic prophylaxis with fondaparinux can be added.

- A weight-adjusted dosage regimen should be considered for pharmacologic thromboprophylaxis in gynecologic surgery patients with obesity.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Mechanical thromboprophylaxis (preferably with intermittent pneumatic compression) generally is sufficient for most patients who undergo minimally invasive gynecologic surgery for benign conditions; however, individualized risk assessment should be considered to determine whether additional prophylaxis is indicated based on patient risk factors for VTE.
- Routine thrombophilia testing should not be performed for patients who experience VTE in the perioperative period. In this setting, assessment of patient risk factors (eg, concurrent hormone exposure) and family history is recommended. For patients with additional risk factors for thrombophilia, VTE, or both, referral to a specialist in thromboembolic disorders should be considered.
- Use of combined hormonal contraceptives is contraindicated in patients undergoing major surgery with anticipated prolonged immobilization. However, if patients are expected to be ambulatory postoperatively, there is no reason to stop combined hormonal contraceptives before surgery.
- Decisions regarding perioperative use of menopausal hormone therapy should be individualized based on clinical risk factors and shared patient–physician decision making.
- Low-molecular-weight heparin prophylaxis should be administered at least 12 hours before neuraxial catheter placement or removal. After neuraxial catheter removal, subsequent administration of LMWH prophylaxis should be delayed at least 4 hours.
- Low-dose unfractionated heparin prophylaxis should be administered 4–6 hours before neuraxial catheter placement or removal. Postoperative low-dose unfractionated heparin prophylaxis can be administered immediately after neuraxial catheter removal.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2007–December 2020. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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