Prevention of Venous Thromboembolic Events After Gynecologic Surgery

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Venous thromboembolic events (deep vein thrombosis [DVT] and pulmonary embolism) are serious preventable complications associated with gynecologic surgery. Preoperative risk assessment of the individual patient will provide insight into the level of risk and the potential benefits of prophylaxis. Common risks include a history of venous thromboembolism, age, major surgery, cancer, use of oral contraceptives or hormone therapy, and obesity. Based on the presence of risk factors, the patient should be categorized into one of four risk groups and appropriate thromboprophylaxis prescribed. Randomized clinical trials in gynecologic surgery and general surgery have established the significant value of thromboprophylaxis. For moderate- and high-risk patients undergoing surgery for benign gynecologic conditions, low-dose unfractionated heparin, low molecular weight (LMW) heparins, intermittent pneumatic leg compression, and graded compression stockings all have demonstrated benefit. If using low-dose unfractionated heparin in high-risk patients, the heparin should be administered 5,000 units every 8 hours. Because DVT often begins in the perioperative period, it is important to initiate low-dose unfractionated heparin or administer the first LMW heparin dose either 2 hours preoperatively or 6 hours after the surgical procedure. Low molecular weight heparin has the advantage of being administered once daily but is more expensive than low-dose unfractionated heparin. In addition, LMW heparin has not been shown to be more effective and has similar risk of bleeding complications when compared with low-dose unfractionated heparin. In the very high-risk patient, a combination of two prophylactic methods may be advisable and continuing LMW heparin for 28 days postoperatively appears to be of added benefit.

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Deep vein thrombosis (DVT) and pulmonary embolism, also referred to as venous thromboembolic events, are two major complications after gynecologic surgery that can result in significant morbidity and mortality.[1] The U.S. Department of Health and Human Services Agency for Healthcare Research and Quality identified the "appropriate use of prophylaxis to prevent venous thromboembolism" as a key safety practice recommendation.[2] Based on randomized clinical trials, appropriate venous thromboembolism prophylaxis would significantly reduce these adverse events. This article will review the available evidence that demonstrates the benefit of prophylaxis. When available, we review trials performed in patients undergoing gynecologic surgery. However, when not available, trials from general surgery are referenced.

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BURDEN OF DISEASE

Two million Americans will develop a DVT each year, and almost one third also will develop a pulmo-

nary embolism, resulting in 60,000 deaths annually[3] The incidence of a first venous thromboembolism is one to two per 1,000 individuals per year.[4,5] The case-fatality rate for pulmonary embolism is 11–12%, although this percentage is higher in patients with cancer and lower in young patients.[5,6]

The prevalence of DVT after gynecologic surgery varies depending on the method used for diagnosis. When I^{125} fibrinogen leg scanning is performed, the DVT prevalence ranges from 15% to 30%. The diagnosis of DVT is approximately 3% when diagnosed clinically and fatal pulmonary emboli occurs in 0.2–0.9% of patients.[1] When diagnosed by I^{125} fibrinogen leg scanning, the incidence of DVT in gynecologic surgery varies widely depending on the risk factors of the individual patient. Approximately 14% of patients undergoing gynecologic surgery for benign indications develop thromboembolism,[7] whereas DVT has been observed in 38% of gynecologic oncology patients postoperatively.[8] The rate of pulmonary embolism in the patient with gynecologic cancer is between 1% and 2.6% and as high as 6.8% in patients with ovarian cancer.[9]

Although many DVTs may be asymptomatic, the presence of a DVT is strongly associated with the development of a symptomatic pulmonary embolism.[1] Death from a pulmonary embolism occurs rapidly with most patients dying within 30 minutes of the first clinical symptoms. Because insufficient time exists for therapeutic interventions for pulmonary embolism, strategies to lower the rate of fatal pulmonary embolism must be directed at preventing the occurrence of DVT. Identification of high-risk patients and institution of consistent, effective thromboprophylaxis can reduce the incidence of this common, often preventable cause of postoperative mortality. Reducing venous thromboembolism will also decrease the associated morbidity of chronic venous stasis changes and ulcers in the lower extremity as well as chronic pulmonary hypertension.

Once a thrombus is formed, the risk of pulmonary embolism depends on the location of the clot. In a prospective study of 382 gynecologic oncology patients, 17% of patients developed DVT as diagnosed by I^{125} fibrinogen scanning. Eighty-five percent of these thrombi were located in the calf veins.[10] In follow-up, nearly one third of these calf thrombi lysed spontaneously, and 65% did not propagate out of the calf during postoperative surveillance. Only 4% propagated to the proximal leg veins, and an additional 4% became symptomatic pulmonary emboli (Fig. 1). These findings emphasize that calf vein thrombosis, although a frequent event, is of minimal clinical significance. Moreover, 40% of the gynecologic oncology patients, who developed postoperative symptomatic pulmonary embolism, had no evidence of DVT in the legs, emphasizing that pelvic vein thrombi pose a high risk of pulmonary embolism.[10]

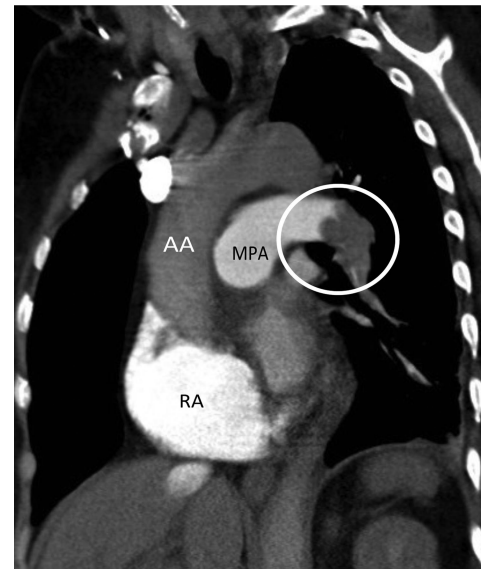

Fig. 1. Computed tomography angiogram of large left pulmonary embolism (sagital oblique reconstruction) pulmonary embolus in oval. AA, ascending aorta; RA, right atrium; MPA, main pulmonary artery. Courtesy of Joseph M. Stavas, MD, Division of Interventional Radiology, University of North Carolina.

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RISK FACTORS FOR VENOUS THROMBOEMBOLISM

In 1858, Virchow reported that the development of thromboembolism is dependent on three factors: hypercoagulability, venous stasis, and vessel wall injury (venous endothelial damage).[11] Patients undergoing gynecologic surgery are predisposed to thromboembolism because of alteration in one or more of these factors. Perioperative and postoperative immobility can adversely affect the drainage of blood from the lower extremity, promoting the development of a DVT.[12] Pelvic masses, a gravid uterus, surgically induced hematomas, or lymphocysts also can lead to venous stasis[10] (Fig. 2). Additionally, vessel wall injury can result from surgical dissection or malignant growth of a tumor into vascular tissues. Coagulation can result from decreased fibrinolytic activity associated with an operative procedure.[13] Elevated coagulation factors (ie, factors I, V, VIII, IX, X, and XI), activated intermediates (antithrombin III complexes),

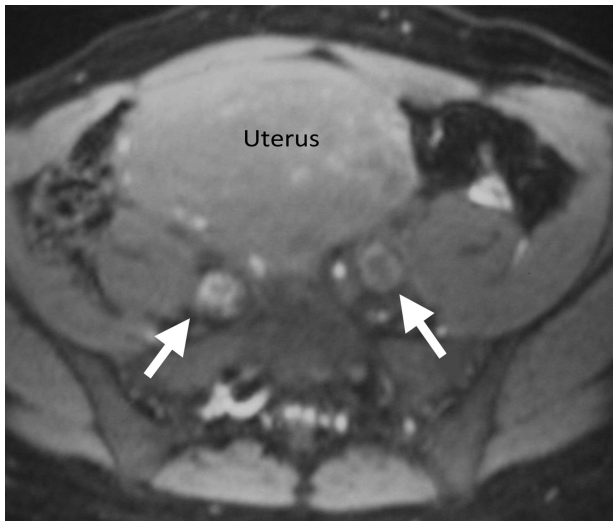

Fig. 2. Pelvic magnetic resonance imaging showing bilateral common iliac venous thrombosis (*arrows*) caused by compression of an enlarged uterus (leiomyomas). Courtesy of Joseph M. Stavas, MD, Division of Interventional Radiology, University of North Carolina.

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and platelet abnormalities contribute to a hypercoagulable state in the gynecologic oncology patient.[14] Cancer cells also secrete procoagulants (eg, tissue factor and cancer procoagulant) as well as factors that affect endothelial permeability (eg, vascular endothelial growth factor) and promote fibrin deposition.[15]

Immobilization is a major risk factor for developing a venous thromboembolism with a ninefold increase seen in patients on bed rest. Hospitalization and surgery are also associated with an increased thrombosis risk with odds ratios (ORs) of 11.1 and 5.9, respectively.[16]

Clinical risk factors in a gynecologic surgery population were assessed in a prospective study of 411 women undergoing major gynecologic surgery for both benign and malignant conditions. These women did not receive any prophylaxis except for early postoperative ambulation. Based on a multivariable analysis, the following clinical findings were identified as independent risk factors: a history of venous thromboembolism, current diagnosis of gynecologic cancer, increasing age, African American race, ankle edema or varicose veins, prolonged surgical time, and prior radiation therapy. High-risk surgical procedures were pelvic exenteration or radical vulvectomy with inguinal–femoral lymphadenectomy.[17]

The risk of venous thromboembolism after gynecologic laparoscopic surgery is uncertain. Some retrospective series of gynecologic laparoscopic procedures reported no venous thromboembolism in more than 75,000 laparoscopic procedures. These reports focused on intraoperative complications and may not have intended to provide information about long-term or perioperative complications.[18,19] Others have reported very low rates of postoperative venous thromboembolism (0–0.3%) and have suggested that venous thromboembolism prophylaxis is not necessary for laparoscopic surgery.[20,21] However, many of the laparoscopic procedures performed in these studies were relatively simple (diagnostic, sterilization, lysis of adhesions, fulguration of endometriosis) in a low-risk population of young women. Studies that have triaged patients by level of surgical complexity have reported a rate of venous thromboembolism for "operative" laparoscopy that is very similar to that reported for open procedures. Harkki-Siren et al reported an overall mortality rate from pulmonary embolism after laparoscopic surgery as 1.0 per 100,000 laparoscopic cases.[22] However, when the mortality rate was calculated to include only total laparoscopic hysterectomies, the death rate was 19.6 per 100,000. Similarly, Nick et al reported that increasing "surgical complexity" resulted in higher rates of venous thromboembolism after laparoscopic procedures.[23]

A retrospective study that was confined to only those women having laparoscopic hysterectomies found an overall 1.0% incidence of clinical venous thromboembolism. However, venous thromboembolism occurred in 2.3%, 2.3%, and 2.9% in patients older than 60 years, who had cancer, or had medical comorbidities, respectively.[24] The only randomized trial comparing outcomes of laparoscopic surgery with open surgery was conducted by the Gynecologic Oncology Group. Patients with endometrial cancer were randomly assigned to undergo hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy by either a laparoscopic or open approach. Two percent of patients in both groups had a clinically significant venous thromboembolism, including fatal pulmonary embolism.[25] Although randomized, prospective data are limited to this one study, it seems reasonable to consider patients who are undergoing complex laparoscopic procedures (including hysterectomy) as at similar risk to those undergoing "open" procedures.

Many environmental, inherited, and acquired risk factors influence coagulability. Hormone therapy and oral contraceptive use are associated with an increased risk of venous thromboembolism. In patients using estrogen plus progestin therapy, the Women's Health Initiative showed a doubling in risk of venous thrombosis from 1.7 to 3.5 events per 1,000

person-years (hazard ratio, 2.1; 95% confidence interval [CI] 1.6–2.7).[26] Tamoxifen use is associated with a similar increase in risk of a major venous thromboembolism (OR 2.1, 95% CI 1.1–4.1).[27] When using estrogen alone, venous thromboembolism risk remains modestly elevated with a hazard ratio of 1.32 (95% CI 0.99–1.75).[28] Although venous thromboembolism is associated with estrogen and progestin use, the overall number of events is low. No trials exist that show a reduction in postsurgical venous thromboembolism with preoperative discontinuation of hormone therapy; thus, this practice cannot be routinely recommended.

Prospectively collected data show a small increase in postoperative venous thromboembolism from 0.5% to 0.96% in oral contraceptive users.[29] Despite a large sample size of more than 17,000 women, this did not reach statistical significance. Venous thromboembolism risk with oral contraceptive use is directly related to estrogen dose with a decreased risk associated with low-estrogen formulations. Prothrombotic clotting factor changes appear to persist for 4–6 weeks after oral contraceptive discontinuation.[30] A systematic review of a high-risk population found that women with thrombophilia were five to 15 times more likely to develop a venous thromboembolism while using oral contraceptives.[31] Discontinuation of oral contraceptives may be a reasonable choice in patients at especially high risk to develop postsurgical venous thromboembolism, but no data exist to support this as a general practice. Thromboprophylaxis should be considered for patients taking oral contraceptives because of the increased risk of venous thromboembolism.

Identified in 1993 as the major cause of activated protein C resistance, factor V Leiden is the most common inherited thrombophilia and is carried by 5% of whites.[32,33] Half of patients with thrombophilia and 20% of patients with venous thromboembolism carry this mutation. Heterozygotes have a threefold to eightfold increase of venous thromboembolism, whereas homozygotes are more severely affected with a 50-fold to 80-fold increase in risk.[34] Prothrombin 20210A mutation is another common mutation found almost exclusively in whites and in 6% of patients with venous thromboembolism. This mutation causes an abnormally elevated prothrombin level, which results in a venous thromboembolism rate three times higher than baseline.[35] Factor V Leiden mutation and prothrombin mutation may be diagnosed by DNA analysis; factor V Leiden mutation can also be detected in an abnormal activated protein C resistance assay. Most inherited factors do not result in venous thromboembolism formation until a precipitating event such as pregnancy, surgery, or exogenous hormone use occurs.[31] The most common mutations found in patients with a venous thromboembolism are factor V Leiden mutation and prothrombin gene mutation G20210A. Presence of one of these conditions in the setting of pregnancy or major surgery confers an elevated venous thromboembolism risk and may place a patient into the highest risk category. A comprehensive summary of risk factors for venous thromboembolism is listed in Box 1.

RISK STRATIFICATION

Patients should be classified preoperatively into one of four risk categories to determine the appropriate thromboprophylaxis regimen. Venous thromboembolism risk is determined based on procedure type and duration, age, and presence of other risk factors. American College of Chest Physicians Guidelines and the American College of Obstetricians and Gynecologists Practice Bulletin suggest stratification of risk based on factors listed in Table 1. Not only do patients have different risk factors, but also not all

Box 1. Venous Thromboembolism Risk Factors

Surgery
Trauma (major or lower extremity)
Immobility, paresis
Malignancy
Cancer therapy (hormonal, chemotherapy, or radiotherapy)
Venous compression (tumor, hematoma, arterial abnormality)
Previous venous thromboembolism
Increasing age
Pregnancy and the postpartum period
Estrogen-containing oral contraception or hormone replacement therapy
Selective estrogen receptor modulators
Erythropoiesis-stimulating agents
Acute medical illness
Inflammatory bowel disease
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Nephrotic syndrome
Obesity
Central venous catheterization
Inherited or acquired thrombophilia

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Table 1. Risk Classification and Recommended Thromboprophylaxis

Level of Risk	Definition	Suggested Thromboprophylaxis Options
Low	Minor surgery (less than 30 min) or noncomplex laparoscopic surgery in patients with no additional risk factors*	Early, frequent ambulation
Moderate	Minor or laparoscopic surgery in patients with additional risk factors; major gynecologic surgery for benign disease and no additional risk factors	LMW heparin or low-dose unfractionated heparin, 5,000 units twice a day, or intermittent pneumatic compression or graduated compression stockings
High	Major surgery in patients with additional risk factors; major surgery in patients with malignancy	LMW heparin or low-dose unfractionated heparin, 5,000 units three times a day, or intermittent pneumatic compression Alternative considerations include a combination of low-dose unfractionated heparin or LMW heparin plus mechanical prophylaxis with graduated compression stockings or intermittent pneumatic compression
Highest	Major surgery in patients older than 60 y with cancer, a prior venous thromboembolism, or both	LMW heparin or low-dose unfractionated heparin, 5,000 units three times a day, plus intermittent pneumatic compression or graduated compression stockings Consider continuing LMW heparin prophylaxis for up to 4 wk after discharge

LMW, low molecular weight.
* Risk factors are listed in Box 1.
Data from Geerts WH, Bergqvist D, Pineo GR, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism. American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest 2008;133(suppl):381S–453S; and Prevention of deep vein thrombosis and pulmonary embolism. ACOG Practice Bulletin No. 84. American College of Obstetricians and Gynecologists. Obstet Gynecol 2007;110:429–40.

prophylactic regimens are appropriate or effective in certain risk groups. The proper risk classification is therefore important to prescribe the best prophylaxis regimen. Additionally, there are certain risk factors that are associated with an especially high risk of developing venous thromboembolism. A retrospective review of more than 1,800 patients identified age older than 60 years, presence of cancer, and history of DVT as being closely associated with postoperative venous thromboembolism, despite the use of intermittent pneumatic compression prophylaxis.[36] Women with two or three of these risk factors had a 3.2% incidence of clinically significant venous thromboembolism compared with an incidence of 0.6% in women who had none or one risk factor. Consideration for more intense prophylaxis is warranted in this highest-risk population.

PREVENTION OF POSTOPERATIVE VENOUS THROMBOEMBOLISM

Rates of venous thromboembolism after gynecologic surgery are similar to those reported in the general surgery literature and average approximately 16% when diagnosed by I^{125} fibrinogen scanning in an untreated population.[37] Graded compression stockings, intermittent pneumatic compression devices, low-dose unfractionated heparin, and low molecular weight (LMW) heparins have each been shown to effectively reduce venous thromboembolism development. Three randomized controlled trials have shown that the use of low-dose unfractionated heparin reduces venous thromboembolism in patients undergoing surgery for benign gynecologic indications[38–40] and in patients with gynecologic cancer.[41] It should be noted, however, that although low-dose unfractionated heparin administered every 12 hours was effective for patients with benign gynecologic conditions, this regimen was not effective for patients with gynecologic cancer.[42] Intermittent pneumatic compression has also been shown to reduce the incidence of venous thromboembolism in a gynecologic oncology patient population.[43] Low molecular weight heparin has not been evaluated in a controlled trial of gynecologic surgery patients. However, trials comparing LMW heparin with low-dose unfractionated heparin have demonstrated equivalent efficacy and similar bleeding complications. A combined regimen of medical and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients. Although limited data exist to support this approach in gynecology patients, studies from the general surgical and neurosurgical literature suggest significant benefit

from a combined regimen. Until more evidence is accumulated, patients undergoing laparoscopic surgery should be stratified by risk category and provided prophylaxis, similar to patients undergoing laparotomy.

PROPHYLAXIS OPTIONS

Deep vein thrombosis and pulmonary embolism can be reduced significantly by a number of prophylactic methods. There are two types of prophylactic options: mechanical and pharmacologic methods. Mechanical methods reduce venous stasis and may promote endogenous fibrinolysis. Pharmacologic methods prevent clot formation by affecting different points on the clotting cascade. Cost, benefit, risk, compliance, patient satisfaction, and feasibility of each method must be weighed in determining the appropriate prophylaxis for an individual patient.

Graduated Compression Stockings

Most postoperative thrombi begin in the capacitance veins of the calf and develop within 24 hours of surgery.[17] In addition to early postoperative ambulation and elevating the foot of the bed, graduated compression stockings prevent pooling of blood in the calves. Based on five randomized controlled trials (one performed in a gynecologic surgery population[44]), a Cochrane review found a 36% reduction in DVT formation with graduated compression stockings, although graduated compression stockings were more effective when combined with a second prophylactic method.[45] Low cost and simplicity are the main advantages of using graduated compression stockings. Correct fit is essential, because tight or improperly fitted stockings can cause an increase in venous stasis by acting as a tourniquet at the knee or midthigh.[46] Knee-length graduated compression stockings are as effective as thigh length and should be preferentially used.[47]

Intermittent Pneumatic Compression

Intermittent pneumatic compression devices regularly compress the calf or calf and thigh with an inflatable pneumatic sleeve, thereby reducing venous stasis. Two randomized controlled trials have been performed in patients undergoing gynecologic surgery. The majority of the patients studied had surgery for gynecologic malignancy. In one trial, intermittent pneumatic compression was placed on the legs at the beginning of surgery and discontinued the next day once the patient was ambulatory. The incidence of 125 fibrinogen scan-detected thrombi was the same in both the control and treatment groups.[43] A subsequent study showed that if the intermittent pneumatic compression device was left on for 5 days or until hospital discharge, there was a significant reduction in the incidence of DVT from 34.6% (control group) as compared with 12.7% (intermittent pneumatic compression group) ($P<.005$).[48]

The benefit of intermittent pneumatic compression in patients undergoing gynecologic surgery appears to be similar to the 69% (CI 0.51–0.72) risk reduction found in 11 randomized controlled studies of intermittent pneumatic compression in other surgical patients.[49]

Patient acceptance of intermittent pneumatic compression is excellent (74%) although similar to patient satisfaction with the administration of LMW heparin.[50] Furthermore, a positive cost–benefit analysis for the use of intermittent pneumatic compression has been demonstrated in gynecologic and general surgery populations.[51,52]

When used during and after major gynecologic surgery, intermittent pneumatic compression devices appear to be as effective as low-dose unfractionated heparin and LMW heparin in reducing DVT incidence.[53–55] Most studies have included a small number of patients and are underpowered to prove efficacy in lowering pulmonary embolism incidence or mortality. The benefits of intermittent pneumatic compression have been postulated to include an increase in systemic fibrinolysis.[56,57] However, larger series have failed to confirm this finding.[58,59]

A wide variety of compression systems exists that use different techniques and sequences of compression. When three commonly used devices were compared, there were significant differences in compression profiles, peak venous-emptying velocity, and total blood expelled from the leg in 1 hour.[60] It is unclear whether these differences are clinically significant because all types appear to successfully prevent stasis in the lower limbs.[61] Another important factor in the reduction of DVT formation using intermittent pneumatic compression devices is compliance with properly applying the device and ensuring a working pump. As part of a randomized clinical trial, compliance was found to be 90%.[50] However, in routine clinical practice, there is likely to be less compliance. When studied in an intensive care setting, the intermittent pneumatic compression devices were properly applied and functional 82% of the time. However, on a regular nursing unit, compliance dropped to 33%.[62] The amount of time per day when intermittent pneumatic compression will result in maximum benefit in venous thromboembolism reduction is unknown.

Low-Dose Unfractionated Heparin

Low-dose unfractionated heparin is the most extensively studied method of thromboprophylaxis. When administered subcutaneously starting 2 hours before surgery and continued every 8–12 hours postoperatively, numerous controlled trials have found low-dose unfractionated heparin effective in preventing DVT.[1] Two large meta-analyses of randomized clinical trials in general surgery patients showed a two-thirds reduction in fatal pulmonary embolism with the use of low-dose unfractionated heparin every 8 hours over placebo or no prophylaxis.[17,63] Patients undergoing major gynecologic surgery for benign indications had a reduction in postoperative DVT when low-dose unfractionated heparin was given in a preoperative dose and postoperatively at 12-hour intervals.[1]

None of these trials were powered to detect a reduction in the incidence of pulmonary embolism. However, giving low-dose unfractionated heparin every 12 hours postoperatively was found to be ineffective in higher-risk patients with gynecologic cancer.[41] In a subsequent trial, the administration of 5,000 units of heparin beginning 2 hours preoperatively and every 8 hours postoperatively did provide effective DVT prophylaxis in women at high risk with gynecologic malignancies.[42]

Advantages of low-dose unfractionated heparin include well-studied efficacy and low cost. A major concern with perioperative low-dose unfractionated heparin use is the potential for increased intraoperative and postoperative bleeding complications. Although surgical blood loss does not seem to be affected by preoperative low-dose unfractionated heparin administration, an increase in postoperative bleeding has been noted, specifically with injection site and wound hematoma formation. Approximately 6% of patients receiving low-dose unfractionated heparin will experience heparin-induced thrombocytopenia.[64] It is recommended that platelet counts be monitored every other day between postoperative days 4 and 14 or until low-dose unfractionated heparin is discontinued. Patients who have received heparin (even heparin flushes of intravenous lines) within 100 days are at significantly higher risk for heparin-induced thrombocytopenia and therefore should have a preoperative baseline platelet count and a repeat platelet count 24 hours after starting low-dose unfractionated heparin.[65]

Low Molecular Weight Heparins

Since initial reports in 1985, multiple well-designed trials have shown LMW heparin to be a reliable method of thromboprophylaxis in many surgical populations, including gynecologic surgery for benign gynecologic conditions[66,67] and surgery for gynecologic cancer.[68–72]

Advantages of LMW heparins include greater bioavailability and once-daily dosing. These benefits result from a longer half-life and more predictable pharmacokinetics. Low molecular weight heparin has more antifactor Xa and less antithrombin activity than low-dose unfractionated heparin, which may decrease medical bleeding and wound hematoma formation. However, LMW heparin is more expensive than low-dose unfractionated heparin. Heparin-induced thrombocytopenia is very rarely observed with LMW heparins, and screening for this is not necessary.[65]

A Cochrane review of randomized, controlled trials in gynecologic patients undergoing major surgery and a systematic analysis of gynecologic oncology patients found LMW heparin and low-dose unfractionated heparin equally useful in preventing DVT.[73,74] Equivalent risk reductions were seen with the use of preoperative and daily postoperative LMW heparin when compared with low-dose unfractionated heparin [66–72] or intermittent pneumatic compression devices.[53] Furthermore, there does not appear to be any difference between LMW heparin and low-dose unfractionated heparin with regard to bleeding complications in these studies. Other considerations regarding the selection of low-dose unfractionated heparin or LMW heparin might include the increased patient discomfort of injections more than once a day and the additional demands on nursing staff.

Renal function should be considered when selecting and dosing an anticoagulant, because many of these agents, including LMW heparin, are renally excreted. Reduced renal clearance is typically defined as glomerular filtration rate less than 30 mL/min. If renal clearance is impaired, drug accumulation may occur, resulting in an increased risk of bleeding. The extent of drug accumulation varies by type of LMW heparin with enoxaparin accumulating rapidly in patients with renal insufficiency. Conversely, dalteparin and tinzaparin showed no evidence of elevated levels when given at prophylactic doses.[75,76] Other anticoagulants that do not require dose adjustment for renal insufficiency include vitamin K antagonists, unfractionated heparin, and argatroban, a small molecule direct thrombin inhibitor. Lepirudin is another direct thrombin inhibitor, but it is renally excreted, so it should not be used in renal failure.[77]

Although it is more frequent to see increased levels of antifactor Xa activity when enoxaparin is used at therapeutic doses, it seems reasonable to start

prophylaxis with a reduced dose (30 units daily) and monitor antifactor Xa activity.

TIMING AND DURATION OF VENOUS THROMBOEMBOLISM PROPHYLAXIS

Because the majority of DVTs form in the operating room and within 24 hours of surgery, it has been the practice in most clinical trials to initiate thromboprophylaxis preoperatively. However, concerns over intraoperative and postoperative bleeding have led many surgeons to delay administration of pharmacologic thromboprophylaxis until postoperatively. The debate centers around the increased risk of intraoperative bleeding if low-dose unfractionated heparin or LMW heparins are administered preoperatively as compared with the efficacy in reducing venous thromboembolism. There is but one randomized trial in patients undergoing elective hip surgery. In that trial, dalteparin was administered at a reduced dose of 2,500 international units 2 hours preoperatively or beginning 6 hours postoperatively. The usual dose of 5,000 international units was started the day after surgery in both groups. The incidence of venous thromboembolism was similar in both groups, whereas bleeding complications were more frequent in the patients who received dalteparin 2 hours preoperatively.[78] Subsequently, a systematic review showed that administering LMW heparin more than 12 hours preoperatively or 12 hours postoperatively resulted in less efficacious venous thromboembolism prevention. However, administration less than 2 hours before surgery was associated with an increase in major bleeding. Based on limited data, the authors have recommended that the optimal timing in which to prevent venous thromboembolism would be to administer LMW heparin up to 2 hours preoperatively or beginning 6 hours postoperatively.[79] It is recognized that elective hip surgery has a very high risk of venous thromboembolism as well as bleeding complications. Therefore, it may be unreasonable to extrapolate the results of patients having hip surgery to women undergoing gynecologic surgery. There are no randomized trials in gynecologic surgery that address the issue of timing of initiating low-dose unfractionated heparin or LMW heparin. One large retrospective study of 9,949 women undergoing hysterectomy for benign conditions concluded that postoperative rather than preoperative administration of low-dose unfractionated heparin or LMW heparin may reduce the risk of bleeding complications after hysterectomy without apparent risk of increased venous thromboembolism. A number of important variables were not controlled for or reported, including the type of drug, drug dose, and time the prophylaxis was administered. Furthermore, the incidence of venous thromboembolism in both groups of patients was extremely low (0.03% DVT; 0.08% pulmonary embolism) not allowing for multivariable analysis.[80] Until randomized trials comparing differences in outcomes when low-dose unfractionated heparin or LMW heparin are administered preoperatively and at fixed times postoperatively, it seems reasonable to follow the guidelines suggesting that the optimal timing to initiate thromboprophylaxis is no less than 2 hours preoperatively or beginning 6 hours postoperatively.

Duration of thromboprophylaxis should also be considered because many venous thromboemboli occur after hospital discharge (when prophylaxis usually is terminated). The incidence of "delayed" venous thromboembolism appears to vary depending on risk factors. Forty percent of patients with cancer who develop a venous thromboembolism will do so more than 21 days after surgery.[81] In a study of patients undergoing gynecologic cancer surgery, 76% of venous thromboemboli were diagnosed after postoperative day 7.[82] Major risk factors for the development of a clinical venous thromboemboli include age older than 60 years, cancer, prior venous thromboembolism, and prolonged surgery or bed rest.[36,81] Five placebo-controlled trials have investigated the value of prolonged LMW heparin prophylaxis (28 days) in preventing venous thromboembolism in high-risk patients. In general, the patients underwent open abdominal surgery for malignancy. Included in these trials were women with gynecologic cancers, although it is not possible to analyze their results separately. A Cochrane Collaboration meta-analysis found an incidence of venous thromboembolism of 14.3% in the control group (in hospital prophylaxis only) as compared with a 6.1% incidence of venous thromboembolism in the group treated for 28 days (OR 0.41, 95% CI 0.26–0.63; $P<.001$). There was no significant difference in both major and minor bleeding between the control group (3.7%) and the group treated with LMW heparin for 28 days (4.1%).[83] Although there are no randomized trials in a gynecologic surgery population, it seems reasonable to consider extending LMW heparin prophylaxis for 28 days in the highest risk patients.

ANESTHESIA CONCERNS

The use of spinal and epidural anesthesia in patients receiving pharmacologic thromboprophylaxis may be a cause for concern as the risk of spinal hematoma with LMW heparin use was underscored by a 1997 public health advisory released by the U.S. Food and Drug Administration. It described 41 patients who developed epidural or spinal hematomas with resul-

tant long-term neurologic injury after using enoxaparin and undergoing epidural or spinal anesthesia (U.S. Department of Health and Human Services. FDA Public Health Advisory. Subject: Reports of epidural or spinal hematomas with concurrent use of low molecular weight heparin and spinal/epidural anesthesia or spinal puncture. Rockville [MD]: Food and Drug Administration; December 1997.).

Many of these patients had multiple risk factors, including additional antithrombotic drug use and vascular or anatomic spinal abnormalities. Additional risk factors for the development of a spinal hematoma include an underlying coagulopathy, traumatic or repeated catheter insertion, advanced age, female gender, and catheter removal while receiving prophylactic or therapeutic anticoagulation.[1]

Although these risk factors are relatively common, development of a spinal hematoma is a rare event and limited data exist to guide evidence-based recommendations. However, the American College of Chest Physicians suggests that spinal and epidural anesthesia be avoided in patients with a bleeding disorder or recent use of antithrombotic drugs, including low-dose unfractionated heparin, LMW heparin, platelet inhibitors such as clopidogrel and ticlopidine, and vitamin K antagonists such as warfarin. Use of nonsteroidal drugs and aspirin has not been linked to spinal hematoma formation. Before neuraxial anesthesia, platelet inhibitors should be discontinued for 5–14 days, low-dose unfractionated heparin for 8–12 hours, and daily LMW heparin for at least 18 hours. Additionally, anticoagulant prophylaxis should be delayed for a hemorrhagic aspirate and for 2 hours after removal of an epidural or spinal catheter. Epidural and spinal catheters should be removed during the nadir of the anticoagulant effect, just before the next scheduled dose of low-dose unfractionated heparin or LMW heparin.[1]

DUAL PROPHYLAXIS

The combined use of two prophylactic methods would potentially further reduce the incidence of venous thromboembolism by attacking two arms of Virchow's triad simultaneously. This approach has been examined in the general surgical and orthopedic literature. A Cochrane review of colorectal surgery showed that low-dose unfractionated heparin combined with graduated compression stockings was four times more effective at venous thromboembolism prevention than low-dose unfractionated heparin alone.[84] In another Cochrane review, various combinations of prophylactic methods were compared with a single prophylaxis. In all comparisons, the combination resulted in significantly reduced venous thromboembolism[85] (Table 2).

Table 2. Comparison of Single and Dual Prophylaxis Outcomes

Treatment	Pulmonary Emboli	Deep Vein Thrombosis
Compression	2.66	4
Compression plus anticoagulation	1.06	1.5
OR (CI)	0.39 (0.25–0.63)	0.43 (0.24–0.76)
Anticoagulant	0	4.21
Anticoagulant plus compression	0	0.65
OR (CI)		0.16 (0.07–0.34)

OR, odds ratio; CI, confidence interval.
Data are percent unless otherwise noted.
Compression: intermittent pneumatic compression±graded compression stockings; anticoagulation: low-dose unfractionated heparin every 12 hours or low-molecular-weight heparin.
Data from Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby GP, Reddy DJ. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. Cochrane Database of Systematic Review 2008; Issue 4. Art. No.: CD005258. DOI: 10.1002/1451858.CD005258.Pub 2.

There are no randomized trials of dual prophylaxis in gynecologic surgery. However, in a retrospective, historically controlled study, Einstein reported that the incidence of venous thromboembolism in a gynecologic oncology population was 1.9% when a combination of intermittent pneumatic compression and low-dose unfractionated heparin (every 8 hours) or LMW heparin were given in combination. In the prior year, patients received only intermittent pneumatic compression and had a venous thromboembolism incidence of 6.5%. The addition of low-dose unfractionated heparin or LMW heparin did not result in increased bleeding complications.[86]

In a retrospective evaluation of 1,892 patients who were treated with intermittent pneumatic compression alone, the presence of two of three identified risk factors (age older than 60 years, cancer, prior venous thromboembolism) places patients in the highest risk category for the development of venous thromboembolism.[36] As a result, the use of a combined approach possesses inherent appeal, because it may reduce both hypercoagulability and venous stasis in highest-risk surgical patients. A decision analysis in high-risk gynecologic oncology patients determined that combined intermittent pneumatic compression and LMW heparin use is cost-effective.[87]

SELECTION OF VENOUS THROMBOEMBOLISM PROPHYLAXIS

Table 2 outlines the general description of levels of risk for individual patients as well as recommended prophylactic measures. These recommendations are based on limited randomized trials in gynecologic surgery and extrapolated from a much larger literature in general and orthopedic surgery.[1,88] It is acknowledged that until there are more randomized clinical trials investigating the value of dual prophylaxis and prolonged prophylaxis, the clinician should use his or her best judgment as to the potential benefits, risks, and costs of various prophylactic regimens.

CONCLUSION

Deep vein thrombosis and subsequent pulmonary embolism are a significant source of morbidity and mortality in gynecologic surgery. Most patients experiencing fatal thromboembolism are diagnosed at autopsy. Prophylaxis against DVT therefore should be used in an effort to decrease the incidence of pulmonary embolism. Each patient should be assessed for thromboembolic risk. Women at low risk benefit from early ambulation. Moderate- and high-risk patients should be treated with low-dose unfractionated heparin, LMW heparin, graduated compression stockings, or intermittent pneumatic compression. Despite evidence that low-dose unfractionated heparin and LMW heparin are associated with increased risk of bleeding, the risk–benefit ratio supports their use in all patients who do not have a contraindication to pharmacologic prophylaxis. All regimens have been found to be cost-effective. The risk of complex laparoscopic surgery approaches the same procedure performed "open" and patients should be prescribed appropriate prophylaxis. In high-risk patients, low-dose unfractionated heparin should be administered at 5,000 units every 8 hours and all prophylaxis should continue throughout the hospital stay. Highest-risk patients (ie, older than 60 years, history of DVT or pulmonary embolism, presence of cancer) may benefit from dual prophylaxis and prolonged (28 days) prophylaxis.

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