Published in final edited form as:

Int J Gynecol Cancer. 2013 November ; 23(9): 1684–1691. doi:10.1097/IGC.0b013e3182a80aa7.

Incidence and Predictors of Venous Thromboembolism After Debulking Surgery for Epithelial Ovarian Cancer

Bahareh Mokri, MD^{*}, Andrea Mariani, MD^{*}, John A. Heit, MD[†], Amy L. Weaver, MS[‡], Michaela E. McGree, BS[‡], Janice R. Martin, RN[‡], Maureen A. Lemens, RN, BSN[§], William A. Cliby, MD^{*}, and Jamie N. Bakkum-Gamez, MD^{*}

^{*}Division of Gynecologic Surgery, Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN

[†]Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, MN

[‡]Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN

[§]Department of Health Sciences Research, and Department of Surgery, Mayo Clinic, Rochester, MN

Abstract

Objective—The aim of this study was to determine the incidence and the risk factors of venous thromboembolism (VTE) within 30 days after primary surgery for epithelial ovarian cancer (EOC).

Methods—In a historical cohort study, we estimated the postoperative 30-day cumulative incidence of VTE among consecutive Mayo Clinic patients undergoing primary cytoreduction for EOC between January 2, 2003, and December 29, 2008. We tested perioperative patient characteristics and process-of-care variables (defined by the National Surgical Quality Improvement Program, >130 variables) as potential predictors of postoperative VTE using the Cox proportional hazards modeling.

Results—Among 569 cases of primary EOC cytoreduction and/or staging and no recent VTE, 35 developed symptomatic VTE within 30 days after surgery (cumulative incidence = 6.5%; 95% confidence interval, 4.4%–8.6%). Within the cohort, 95 (16.7%) received graduated compression stockings (GCSs), 367 (64.5%) had sequential compression devices + GCSs, and 69 (12.1%) had sequential compression devices + GCSs + postoperative heparin, with VTE rates of 1.1%, 7.4%, and 5.8%, respectively ($P = 0.07$, χ^2 test). The remaining 38 (6.7%) received various other chemical and mechanical prophylaxis regimens. In the multivariate analysis, current or past tobacco smoking, longer hospital stay, and a remote history of VTE significantly increased the risk for postoperative VTE.

Conclusions—Venous thromboembolism is a substantial postoperative complication among women with EOC, and the high cumulative rate of VTE within 30 days after primary surgery suggests that a more aggressive strategy is needed for VTE prevention. In addition, because longer hospital stay is independently associated with a higher risk for VTE, methods to decrease length of stay and minimize factors that contribute to prolonged hospitalization are warranted.

Keywords

Venous thromboembolism; Deep vein thrombosis; Ovarian cancer; Surgery

Venous thromboembolism (VTE) related to malignancy is a serious life-threatening event that is associated with poorer outcomes.¹ Deep venous thrombosis (DVT) with or without pulmonary embolism (PE) is a common complication of malignancy, including epithelial ovarian cancer (EOC),^{2,3} and is the second most common cause of mortality in cancer patients.⁴ In fact, patients with an active malignancy experience fatal PE more often than the general population.⁵ Although an increase in VTE rate is observed in advanced breast, lung, pancreatic, and hepatobiliary cancers, advanced disease also increases the risk for PE in EOC.⁵ Among metastatic cancers in general, the rate of VTE in EOC is similar to that observed in gastric, lung, pancreatic, and hematologic malignancies, with VTE occurring in up to 29% of cases.⁴ Reported risk factors of thrombosis related to gynecological cancers have included pelvic surgery, age, race, previous leg edema, presence of venous varicosities, history of VTE, longer duration of surgery, receipt of chemotherapy or radiation therapy, and immobility.^{6,7}

Approximately one third of postoperative VTEs in cancer patients occur after discharge from the hospital.⁸ It has been postulated that this is because VTE prophylaxis is given to most cancer patients during their hospitalization but is discontinued after discharge from the hospital.⁹ In gynecologic cancer patients, up to 75% of VTE events are diagnosed after the first postoperative week.² In addition, the diagnosis of EOC; having a personal history of VTE; age older than 60 years; surgical duration of more than 2 hours; bed rest of more than 4 days; prolonged hospital stay; and postoperative complications such as sepsis, urinary tract infection, transfusion, myocardial infarction, and pneumonia are associated with an increase in the risk for being diagnosed with a VTE.^{2,10} Both perioperative prophylactic measures^{10,11} and extended prophylaxis with low molecular-weight heparin (LMWH) for 4 weeks after surgery for pelvic or abdominal malignancy¹² have been shown to decrease VTE. However, reimbursement for prolonged prophylaxis can be problematic. In this study, we aimed to estimate the incidence of VTE within 30 days after surgical debulking for primary EOC and to determine the risk factors of VTE after surgery for EOC.

Methods

Study Population, Setting, and Design

All women undergoing primary cytoreduction for EOC, primary peritoneal carcinoma, or fallopian tube carcinoma (all collectively referred to as “EOC” for this study) at the Mayo Clinic (Rochester, MN) between January 2, 2003, and December 29, 2008, were identified retrospectively. Cases were identified using the *International Classification of Diseases*,

Ninth Revision, codes for EOC, primary peritoneal carcinoma, and fallopian tube carcinoma (183.0, 183.2, 183.8, 158.8, and 158.9) and surgical staging and debulking procedures (68.3, 68.4, 68.5, 68.6, 68.7, 68.8, 68.9, 65.61, 65.63, 40.29, 40.3, 40.59, and 54.4). Patients were excluded if they had received neoadjuvant therapy, were being treated for recurrent disease, underwent previous surgery for their cancer, had nonepithelial or nonovarian malignancy, did not consent to the use of their medical records for research purposes, or had a VTE event within 30 days before their EOC surgery. As a historical cohort study, all eligible women were followed forward in time from the date of surgery (index date) to the first symptomatic DVT and/or PE event, death, or the last follow-up or 30 days from the index date, whichever came first. This study was approved by the Mayo Clinic institutional review board.

Measurements

Perioperative variables defined by the American College of Surgeons National Surgical Quality Improvement Program were abstracted by a trained, dedicated registered nurse abstractor using an explicit data collection instrument. The variables included patient age and body mass index (BMI) at the time of surgery; American Society of Anesthesiologists (ASA) score; personal history of nonovarian cancer; smoking history (current/past vs never); ascites; operative time; histology; International Federation of Gynecology and Obstetrics (FIGO) stage; operative complexity (Table 1)¹³; residual disease (RD); estimated blood loss; perioperative VTE prophylaxis type; hospital length of stay (LOS); postoperative complications; and preoperative comorbidities including, but not limited to, previous VTE. Non-VTE postoperative complications during the initial hospitalization had to have occurred before the VTE to be considered as a potential risk factor in the analysis. Venous thromboembolism was defined as a clinically diagnosed DVT or PE. Venous thromboembolisms diagnosed within the Mayo system were verified by imaging or autopsy; outside medical summaries were used to confirm VTEs diagnosed at non-Mayo facilities. Screening for subclinical VTEs was not performed. Venous thromboembolisms were managed with therapeutic anticoagulation according to clinical guidelines contemporary at the time of VTE diagnosis.

Venous thromboembolism prophylaxis was administered according to surgeon preference. Retrospectively, the prophylaxis regimens were classified into 3 groups: (1) graduated compression stockings (GCSs) alone, (2) sequential compression devices (SCDs) + GCSs, and (3) SCDs + GCSs + postoperative only unfractionated heparin or LMWH. Graduated compression stockings and SCDs were both placed before surgery and continued throughout the length of hospital stay.

Statistical Analyses

The outcome of interest was the development of postoperative VTE within 30 days after primary EOC surgical cytoreduction. Patients with VTE diagnosis within 30 days before EOC surgery were excluded. Data were summarized using standard descriptive statistics. Duration of follow-up was calculated from the date of the EOC surgery to the date of the first VTE within 30 days; otherwise, for the patients without a VTE within 30 days, the patients' follow-up was censored at the date of their last relevant clinical follow-up if within 30 days or at day 31 if the patient had more than 30 days of follow-up. The Kaplan-Meier

method was used to estimate the cumulative incidence of VTE within 30 days. Baseline patient characteristics were evaluated for an association with VTE within 30 days after surgery by fitting separate Cox proportional hazard regression models, thereby taking into account the timing of the VTE and varying duration of follow-up within the first 30 days. Length of initial hospitalization was evaluated as a binary time-dependent covariate that denoted whether the patient was still in the hospital as part of the initial hospitalization. Factors with a *P* value of less than 0.20 based on the univariate logistic regression models were considered in the multivariate model building. A parsimonious model was identified using stepwise and backward variable selection. Associations were summarized using hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Analyses were performed using the SAS version 9.2 software package (SAS Institute, Inc, Cary, NC).

Results

Incidence and Timing of VTE Within 30 Days After Primary EOC Surgery

Between January 2, 2003, and December 29, 2008, a total of 587 women underwent surgical cytoreduction and/or staging for primary EOC. Perioperative demographics of this cohort have been previously published.¹⁴ Among these women, 18 (3.1%) were diagnosed with a VTE within 30 days before their cytoreductive surgery and were excluded from further analyses. Among the remaining 569 women, within the first 30 days after surgery, 40 women were diagnosed with a VTE. Seven VTEs were upper extremity DVTs, 3 were associated with a peripherally inserted central catheter line placed in the immediate postoperative period, and 2 were associated with central venous access port placement at the time of cytoreduction surgery. Among the 569 women, only 3 had a central venous access port placed at the time of their debulking procedure. Thus, 2 of 3 of the concomitantly placed ports resulted in upper extremity DVT formation.

The remaining 2 upper extremity DVTs were not associated with a venous access catheter and were included in the subsequent analyses. Thus, 35 women were diagnosed with a VTE not associated with a venous access catheter, for a cumulative incidence of 6.5% (95% CI, 4.4%–8.6%) within 30 days. Among the remaining 534 women, 13 died within the first 30 days and 59 had less than 30 days of available clinical follow-up. The cumulative incidence of VTE within 30 days after surgery is shown in Figure 1. The distribution of the 35 included postoperative VTE events by event type is shown in Table 2. Among the 35 postoperative VTE events, 20 (57.1%) were diagnosed before and 15 (42.9%) were diagnosed after the index surgery hospitalization discharge. The median time to postoperative VTE was 10 days (interquartile range [IQR], 6–17 days). Among the 35 VTE cases, 4 died within 30 days after surgery and an additional 6 died within 6 months.

Among the 569 patients, 95 (16.7%) received GCSs, 367 (64.5%) had SCDs + GCSs, and 69 (12.1%) had SCDs + GCSs + postoperative heparin, with VTE rates of 1.1%, 7.4%, and 5.8%, respectively ($P = 0.07$, χ^2). None of the aforementioned patients received preoperative heparin. The remaining 38 (6.7%) patients had prophylaxis approaches that did not fit into 1 of the 3 prophylaxis groups. Among these, 13 (2.3% of the whole cohort) received a prophylactic dose of unfractionated heparin or LMWH before surgical incision, and dual prophylaxis (SCDs + heparin) was continued in 6 (1.1% of the whole cohort) of those 13

patients after surgery. The remaining 25 patients had various other combinations of mechanical and chemical prophylaxis in the perioperative setting. No patients were dismissed from the hospital on a prophylactic dose of heparin.

Factors Associated With VTE Development Within 30 Days of EOC Surgery

In the univariate Cox regression analyses, current or past tobacco smoking (HR, 2.41 [95% CI, 1.23–4.74]; $P = 0.01$, vs lifelong nonsmoker) and ascites (2.25 [1.05–4.80], $P = 0.04$, vs no ascites) were predictors of postoperative VTE. There was a trend toward a significant association between having a remote history of VTE (>30 days before surgery; 2.76 [0.97–7.81], $P = 0.06$, vs no history of VTE), ASA score of greater than 2 (1.86 [0.94–3.65], $P = 0.07$, vs ASA score 2), operative time (1.18 [0.97–1.43], $P = 0.09$, per 60-minute increment), the presence of RD (1.96 [0.92–4.17] for measurable 1 cm; 2.39 [0.99–5.77] for measurable >1 cm, vs microscopic RD), and serous histology (2.21 [0.86–5.70], $P = 0.10$, vs nonserous histology) and developing a postoperative VTE (Table 3). Patient age, BMI, FIGO stage, estimated operative blood loss, operative complexity, and other past medical co-morbidities (Table 3) were not univariately associated with postoperative VTE.

The median (IQR) length of hospital stay was 8 (6–11) days for those who did not develop VTE. Among the 35 women with VTE, the median (IQR) length of hospitalization before developing the VTE was 8 (6–11) days and the total median (IQR) length of initial hospitalization was 14 (8–18) days. Length of initial hospitalization was evaluated as a binary time-dependent covariate that denoted whether the patient was still in the hospital as part of the initial hospitalization. The women still in the hospital were at a 4-fold increased risk for VTE compared with those no longer in the hospital (HR, 4.48 [95% CI, 1.86–10.77]; $P < 0.001$).

In the univariate analyses of postoperative complications during initial hospitalization as potential risk factors of postoperative VTE, neither the development of a major complication (bowel leak, return to the operating room; HR, 1.34 [95% CI, 0.41–4.38]; $P = 0.63$) nor the development of other postoperative complications (ileus, bowel obstruction, surgical site infection, intra-abdominal abscess, upper respiratory infection, urinary tract infection, cardiac event, or central nervous system event; HR, 1.24 [95% CI, 0.63–2.47]; $P = 0.53$) was significantly associated with an increase in the risk for VTE.

In the multivariate analysis, current or past tobacco smoking (2.46 [1.25–4.87]; $P = 0.01$), having a history of VTE (3.14 [1.10–8.97]; $P = 0.03$), and longer length of hospital stay (4.29 [1.80–10.23]; $P = 0.001$) were independently associated with VTE development within 30 days after surgery (Table 4).

Discussion

Patients with malignancy are at higher risk for VTE and VTE-associated death than are patients without cancer.^{1,5} It is estimated that 1 in 7 deaths in hospitalized patients with malignancy occurs because of PE.¹ In addition, surgical intervention increases VTE risk.¹⁵ Among the independent factors associated with VTE in a population-based study described by Heit et al,¹⁶ most factors, including malignancy, prolonged hospital LOS, chemotherapy,

and the use of central venous catheters, are observed in women undergoing treatment of EOC. In addition, 1 in 12 patients experiencing VTE associated with cancer surgery die within 30 days of their surgery.⁸ Thus, optimizing the approach to thrombosis prevention is critical in the surgical care of women with EOC.

The overall incidence of DVT with and without PE has been reported to range from 10% to 15% in patients with cancer^{7,17} and has been reported to occur in up to 29% of EOC patients with metastatic disease.⁵ The diagnosis of EOC seems to carry with it a greater VTE risk than the diagnosis of other gynecologic malignancies, such as endometrial or cervical cancer.² In a cohort study of more than 4000 gynecologic malignancies, more than 75% of VTEs in gynecologic cancer patients occurred more than 1 week after surgery.² In a nested case-control study of this cohort, Peedicayil et al² demonstrated that a personal history of VTE and hospital LOS of more than 5 days were factors associated with development of VTE within 90 days after gynecologic cancer surgery. Furthermore, the combination of carcinoma of the ovary, the peritoneum, or the fallopian tube and hospital LOS of more than 5 days was associated with a higher rate of VTE within 8 to 28 days after surgery. In addition, in a separate study of general surgical oncology patients, up to 40% of VTEs were diagnosed more than 21 days postoperatively.¹⁸ These findings support the notion that risk for VTE persists even after a patient has become ambulatory and is dismissed from the hospital.

In addition to the perioperative risk factors of venous stasis and endothelial injury,¹⁹ malignant tissues seem to release soluble factors into the peritoneal cavity because of easy penetration of the mesothelium by chemokines and cytokines. Such factors can cause transcriptional changes in the peritoneum and subjacent stroma in EOC and potentially increase coagulability.²⁰ The downstream effects of these coagulation aberrancies can be prevented by heparins because these increase the action of antithrombin on thrombin and factor Xa,²¹ thus preventing one of the final critical steps in clot formation.

In our study, it was not surprising to find that longer hospital LOS, smoking history, and a history of VTE were independently associated with an increased risk for VTE. Longer hospitalizations are likely multifactorial in etiology. Patients who require longer lengths of stay may be less mobile after surgery and have longer durations of venous stasis. In addition, although the development of a postoperative complication was not significantly associated with the ultimate development of a VTE, patients who develop postoperative complications during initial hospitalization may be hospitalized longer for complication management. Another important influence on hospital LOS involves patient and provider expectations. Approaches to enhancing postoperative recovery have been demonstrated to reduce complications and LOS after extensive abdominopelvic surgery for malignancy.^{22–24} Thus, LOS may be a modifiable risk factor of VTE.

Patients with a history of smoking seem to have a higher baseline incidence of VTE. Smoking-associated thrombotic events seem to occur secondary to an increase in thrombopoietin, which provokes platelet activation^{25,26} and the sticky fibrin phenomenon.²⁷ Because these factors increase coagulation, the effect of heparin should theoretically blunt their effects on clotting. The finding that a history of VTE was independently associated

with postoperative VTE development is consistent with previous findings within the gynecologic oncology literature.² Most of those with a history of VTE in our study had a remote history years before their EOC diagnosis. This suggests that these patients had an underlying propensity toward VTE development, and testing for hypercoagulable conditions may be warranted for perioperative and longer-term clinical management of such patients.

Independent factors associated in our study differed, however, from those identified in one of the largest studies of VTE occurrence during primary EOC treatment. Fotopoulou et al²⁸ reported on VTE incidence during the adjuvant chemotherapy setting after primary EOC debulking, and independent risk factors identified during that extended period included BMI of greater than 30 kg/m² and increasing age. Considering the longer duration of observation and additional variable of chemotherapy receipt, extended follow-up of our cohort is warranted to determine whether variables associated with VTE are influenced by the transition to adjuvant chemotherapy.

In our cohort of patients, the cumulative incidence of VTE within 30 days after surgery was 6.5%, and the 30-day rate ranged from 1.1% in those receiving GCSs alone to 7.4% in those receiving prophylaxis with SCDs + GCSs. The overall rate of 6.5% is the same as the rate that Einstein et al²⁹ reported in their gynecologic oncology service before initiating dual perioperative prophylaxis. In their quality improvement project, they initiated a practice change in that patients received a dose of subcutaneous heparin 1 to 2 hours before surgery and had SCDs placed before induction of anesthesia. Postoperatively, 3 times daily of subcutaneous heparin and SCDs were both continued until dismissal. Their rate dropped to 1.9% after converting to perioperative dual prophylaxis. In addition, Clark-Pearson et al¹⁷ have shown that 3 times daily of prophylactic heparin that is initiated before surgical incision in gynecologic cancer patients is superior to twice daily of prophylactic heparin or receiving no prophylaxis. In addition, receipt of heparin in this dosing schedule did not increase postoperative bleeding complications. In our study, various prophylaxis measures were used on the basis of surgeon preference, and only 1.1% of the cohort received perioperative heparin prophylaxis in the methodology described by both Einstein et al²⁹ and Clark-Pearson et al.¹⁷ Among those in our study who received SCDs + GCSs + postoperative heparin (only 12.1% of the cohort), the rate of VTE within 30 days was 5.8%, more than 3 times higher than the rate of 1.9% that Einstein et al²⁹ observed after initiating dual prophylaxis with SCDs and 3 times daily of heparin starting before incision. This suggests that starting heparin prophylaxis after surgery is not as effective as initiation before incision. Indeed, prospective data support the initiation of dual prophylaxis before surgery,^{17,29} and clear guidelines for perioperative prophylaxis and extended-duration (4 weeks after surgery) prophylactic LMWH now exist in high-risk patients undergoing pelvic surgery for malignancy.¹⁰

In addition, placement of long-term central venous access catheters at the time of primary debulking seems to carry a high risk for provoking upper extremity DVT. Among the 7 arm DVTs, more than 70% were associated with a central venous access catheter placed either during the same anesthetic as the debulking procedure or within the same hospitalization. This suggests that judicious use of postoperative peripherally inserted central catheter lines

and delayed placement of implanted venous access catheters are warranted in this high-risk patient population.

A clear limitation to this study is that nearly 87% of the study cohort did not receive in-hospital prophylaxis according to contemporary guidelines.¹⁰ Thus, our findings seem to illustrate the natural history of VTE development after primary EOC debulking surgery. However, since the study period, dual prophylaxis and 4-week extended-duration prophylactic LMWH have been implemented according to published guidelines,¹⁰ and analysis of their impact on VTE incidence is warranted. Other limitations of this study include its retrospective nature and the fact that there were 10% of patients who were lost to follow-up during the first 30 days. However, the 30-day follow-up allowed for close surveillance of the patients in the immediate postoperative period, and the use of a comprehensive electronic medical record allowed for accurate data abstraction that minimized potential bias from missing data.

In summary, an overall cumulative incidence of VTE of 6.5% within 30 days of surgery is unacceptably high. Because prospective data have shown significant reduction in VTE events in gynecologic surgery when subcutaneous heparin is given before surgical incision,^{17,29} we have since implemented this approach to prophylaxis in our patients undergoing surgery for EOC. In addition, heparin prophylaxis for 4 weeks after surgery has also been shown to significantly decrease postoperative VTE after pelvic cancer surgery,¹² and, following current guidelines,¹⁰ this has also been initiated at our institution. Determination of the impact of quality of care of this standardized prophylaxis regimen in postoperative patients with newly diagnosed EOC is warranted. In addition, because the risk for developing a VTE after EOC cytoreduction and staging persists after dismissal and into the adjuvant therapy period,²⁸ further investigation into the duration of VTE risk and duration of postoperative prophylaxis is warranted. Such questions will be explored in a larger EOC cohort with perioperative follow-up extended through completion of their adjuvant chemotherapy.

Acknowledgments

The authors thank Harry J. Long, MD, for his contribution to study design and manuscript review.

Funded, in part, by the Office of Women's Health Research Building Interdisciplinary Careers in Women's Health (BIRCWH award K12 HD065987).

The funding source played no role in the design, conduct, or reporting of this study.

The funding source provided protected research time for Dr Bakkum-Gamez.

References

1. Pruemer J. Prevalence, causes, and impact of cancer-associated thrombosis. *Am J Health Syst Pharm.* 2005; 62:S4–S6. [PubMed: 16286366]
2. Peedicayil A, Weaver A, Li X, et al. Incidence and timing of venous thromboembolism after surgery for gynecological cancer. *Gynecol Oncol.* 2011; 121:64–69. [PubMed: 21183211]
3. Satoh T, Oki A, Uno K, et al. High incidence of silent venous thromboembolism before treatment in ovarian cancer. *Br J Cancer.* 2007; 97:1053–1057. [PubMed: 17895896]

4. Heidrich H, Konau E, Hesse P. Asymptomatic venous thrombosis in cancer patients—a problem often overlooked. Results of a retrospective and prospective study. *Vasa*. 2009; 38:160–166. [PubMed: 19588304]
5. Ma S, Lin Y, Ying H, et al. Solid malignancies complicated with pulmonary embolism: clinical analysis of 120 patients. *Chin Med J (Engl)*. 2010; 123:29–33. [PubMed: 20137571]
6. Clarke-Pearson D, DeLong E, Synan I, et al. Variables associated with postoperative deep venous thrombosis: a prospective study of 411 gynecology patients and creation of a prognostic model. *Obstet Gynecol*. 1987; 69:146–150. [PubMed: 3808500]
7. Ailawadi M, Del Priore G. A comparison of thromboembolic prophylaxis in gynecologic oncology patients. *Int J Gynecol Cancer*. 2001; 11:354–358. [PubMed: 11737465]
8. Merkow RP, Bilimoria KY, McCarter MD, et al. Post-discharge venous thromboembolism after cancer surgery: extending the case for extended prophylaxis. *Ann Surg*. 2011; 254:131. [PubMed: 21527843]
9. Merkow RP, Bilimoria KY, McCarter MD, et al. Postdischarge venous thromboembolism after cancer surgery: extending the case for extended prophylaxis. *Ann Surg*. 2011; 254:131–137. [PubMed: 21527843]
10. Gould MK, Garcia DA, Wren SM, 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. *Chest*. 2012; 141:e227S–e277S. [PubMed: 22315263]
11. Committee on Practice Bulletins—Gynecology, American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 84: prevention of deep vein thrombosis and pulmonary embolism. *Obstet Gynecol*. 2007; 110:429–440. [PubMed: 17666620]
12. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med*. 2002; 346:975–980. [PubMed: 11919306]
13. Aletti GD, Dowdy SC, Podratz KC, et al. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. *Am J Obstet Gynecol*. 2007; 197:676. [PubMed: 18060979]
14. Bakkum-Gamez JN, Langstraat CL, Martin JR, et al. Incidence of and risk factors for postoperative ileus in women undergoing primary staging and debulking for epithelial ovarian carcinoma. *Gynecol Oncol*. 2012; 125:614–620. [PubMed: 22370599]
15. Wong P, Baglin T. Epidemiology, risk factors and sequelae of venous thromboembolism. *Phlebology*. 2012; 27:2–11. [PubMed: 22457300]
16. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med*. 2000; 160:809. [PubMed: 10737280]
17. Clark-Pearson D, DeLong E, Synan IS, et al. A controlled trial of two low-dose heparin regimens for the prevention of postoperative deep vein thrombosis. *Obstet Gynecol*. 1990; 75:684. [PubMed: 2179782]
18. Agnelli G, Bolis G, Capussotti L, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: the @RISTOS Project. *Ann Surg*. 2006; 243:89. [PubMed: 16371741]
19. Kiyomura M, Katayama T, Kusanagi Y, et al. Ranking the contributing risk factors in venous thrombosis in terms of therapeutic potential: Virchow's triad revisited. *J Obstet Gynaecol Res*. 2006; 32:216–223. [PubMed: 16594928]
20. Punnonen R, Teisala K, Kuoppala T, et al. Cytokine production profiles in the peritoneal fluids of patients with malignant or benign gynecologic tumors. *Cancer*. 1988; 83:788–796. [PubMed: 9708947]
21. Lin PH, Sinha U, Betz A. Antithrombin binding of low molecular weight heparins and inhibition of factor Xa. *Biochim Biophys Acta*. 2001; 1526:105–113. [PubMed: 11287128]
22. Anderson ADG, McNaught CE, MacFie J, et al. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg*. 2003; 90:1497–1504. [PubMed: 14648727]

23. Spanjersberg W, Reurings J, Keus F, et al. Fast track surgery versus conventional recovery strategies for colorectal surgery. *Cochrane Database Syst Rev*. 2011; 2:CD007635. [PubMed: 21328298]
24. Wind J, Polle SW, Fung Kon Jin PHP, et al. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg*. 2006; 93:800–809. [PubMed: 16775831]
25. Venge GLP. Platelet adhesion in patients prone to arterial and venous thrombosis: the impact of gender, smoking and heredity. *Scand J Clin Lab Invest*. 1998; 58:279–286. [PubMed: 9741815]
26. Lupia E, Bosco O, Goffi A, et al. Thrombopoietin contributes to enhanced platelet activation in cigarette smokers. *Atherosclerosis*. 2010; 210:314–319. [PubMed: 20006331]
27. Pretorius E, Oberholzer HM, van der Spuy WJ, et al. Smoking and coagulation: the sticky fibrin phenomenon. *Ultrastruct Pathol*. 2010; 34:236–239. [PubMed: 20594045]
28. Fotopoulou C, duBois A, Karavas AN, et al. Incidence of venous thromboembolism in patients with ovarian cancer undergoing platinum/paclitaxel-containing first-line chemotherapy: an exploratory analysis by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group. *J Clin Oncol*. 2008; 26:2683–2689. [PubMed: 18509180]
29. Einstein MH, Kushner DM, Connor JP, et al. A protocol of dual prophylaxis for venous thromboembolism prevention in gynecologic cancer patients. *Obstet Gynecol*. 2008; 112:1091. [PubMed: 18978110]

Figure 1. Thirty-day cumulative incidence of postoperative VTE among women undergoing primary surgery for EOC at the Mayo Clinic, January 2, 2003, to December 29, 2008. The values in parentheses denote the number of patients still at risk at each time point.

Surgical complexity scoring**Table 1**

Procedure	Points
Total hysterectomy + bilateral salpingo-oophorectomy	1
Omentectomy	1
Pelvic lymphadenectomy	1
Para-aortic lymphadenectomy	1
Pelvic peritoneum stripping	1
Abdominal peritoneum stripping	1
Rectosigmoidectomy, T-T anastomosis	3
Large bowel resection	2
Diaphragm stripping and resection Splenectomy	2
Liver resection	2
Small bowel resection	1
Complexity Score Groups	Points
1 – Low	3
2 – Intermediate	4–7
3 – High	8

Adapted from Aletti et al.¹³ T-T, transverse-to-transverse colon.

Table 2
Distribution of postoperative VTE by clinically evident event type

Site of VTE	n	%
Leg DVT alone	5	14.3
Arm DVT alone	2	5.7
PE	25	71.4
PE and leg DVT	3	8.6

Events related to central venous catheters are excluded.

Table 3
Univariate analyses of demographic and baseline characteristics as potential predictors of incident DVT and/or PE among women undergoing primary surgery for EOC at the Mayo Clinic, January 2, 2003, to December 29, 2008

Characteristic	With Postoperative VTE, n (%)	HR (95% CI)*	P*
Age, y			
First quartile (<55.33, n = 142)	6 (4.2)	Reference	0.24 [†]
Second quartile (55.33–63.93, n = 142)	9 (6.3)	1.49 (0.54–4.19)	
Third quartile (63.94–72.15, n = 142)	9 (6.3)	1.51 (0.54–4.25)	
Fourth quartile (≥ 72.16, n = 143)	11 (7.7)	2.02 (0.75–5.46)	
BMI, kg/m ²			
<25 (n = 208)	14 (6.7)	Reference	0.17 [†]
25–29.9 (n = 174)	4 (2.3)	0.33 (0.11–1.00)	
30 (n = 185)	17 (9.2)	1.37 (0.68–2.78)	
ASA score			0.07
2 (n = 308)	14 (4.5)	Reference	
>2 (n = 261)	21 (8.0)	1.86 (0.94–3.65)	
Medical history/comorbidities			
Cardiac event			0.70
Yes (n = 58)	4 (6.9)	1.23 (0.43–3.47)	
No (n = 511)	31 (6.1)	Reference	
Pulmonary disease			0.82
Yes (n = 158)	10 (6.3)	1.09 (0.52–2.27)	
No (n = 411)	25 (6.1)	Reference	
Diabetes mellitus			0.85
Yes (n = 56)	3 (5.4)	0.89 (0.27–2.90)	
No (n = 513)	32 (6.2)	Reference	
Hypertension			0.28
Yes (n = 263)	13 (4.9)	0.68 (0.35–1.36)	
No (n = 306)	22 (7.2)	Reference	
Anemia			0.79
Yes (n = 125)	7 (5.6)	0.90 (0.39–2.05)	
No (n = 444)	28 (6.3)	Reference	
Stroke			0.56
Yes (n = 30)	1 (3.3)	0.55 (0.08–4.01)	
No (n = 539)	34 (6.3)	Reference	
DVT/PE [‡]			0.06
Yes (n = 27)	4 (14.8)	2.76 (0.97–7.81)	
No (n = 542)	31 (5.7)	Reference	
Personal history of nonovarian cancer			0.16
Yes (n = 78)	2 (2.6)	0.36 (0.09–1.50)	

Characteristic	With Postoperative VTE, n (%)	HR (95% CI)*	P*
No (n = 491)	33 (6.7)	Reference	
Smoking history (current/past smoker)			0.01
Yes (n = 223)	21 (9.4)	2.41 (1.23–4.74)	
No (n = 346)	14 (4.0)	Reference	
FIGO stage			0.76
IIIA (n = 443)	28 (6.3)	1.14 (0.50–2.61)	
I or II (n = 126)	7 (5.6)	Reference	
Ascites			0.04
Yes (n = 326)	26 (8.0)	2.25 (1.05–4.80)	
No (n = 243)	9 (3.7)	Reference	
Operative complexity			0.47
Low (n = 101)	4 (4.0)	Reference	
Intermediate (n = 335)	20 (6.0)	1.48 (0.50–4.32)	
High (n = 133)	11 (8.3)	1.99 (0.63–6.24)	
Operative time, min			0.09 [‡]
First quartile (<184, n = 144)	10 (6.9)	Reference	
Second quartile (184–238, n = 141)	6 (4.3)	0.59 (0.22–1.63)	
Third quartile (239–313, n = 142)	1 (0.7)	0.10 (0.01–0.76)	
Fourth quartile (314–387, n = 142)	18 (12.7)	1.78 (0.82–3.86)	
Estimated blood loss, mL			0.15 [‡]
First quartile (<500, n = 131)	4 (3.1)	Reference	
Second quartile (500–749, n = 138)	8 (5.8)	1.94 (0.59–6.45)	
Third quartile (750–1199, n = 141)	11 (7.8)	2.62 (0.83–8.23)	
Fourth quartile (1200–1599, n = 158)	12 (7.6)	2.51 (0.81–7.79)	
RD			0.09
No (n = 307)	13 (4.2)	Reference	
Yes, measurable 1 cm (n = 178)	14 (7.9)	1.96 (0.92–4.17)	
Yes, >1 cm (n = 84)	8 (9.5)	2.39 (0.99–5.77)	
Histology			0.10
Nonserous (n = 149)	5 (3.4)	Reference	
Serous (n = 420)	30 (7.1)	2.21 (0.86–5.70)	
Length of hospitalization	—	4.48 (1.86–10.77) [§]	<0.001

* Results are based on fitting univariable Cox proportional hazards regression models.

[‡] For the continuous scaled variables, the *P* values are based on evaluating the actual continuous scaled variable rather than the BMI classifications or quartiles in each Cox model.

[‡] History of DVT/PE more than 30 days before surgery.

[§] Length of initial hospitalization was evaluated in a univariate Cox regression model as a binary time-dependent covariate that denoted whether the patient was still in the hospital as part of the initial hospitalization. The HR of 4.48 suggests that patients still in the hospital are at a 4-fold increased risk for VTE compared with those no longer in the hospital.

Table 4
Multivariate analyses of demographic and baseline characteristics as potential predictors of incident DVT and/or PE among women undergoing primary surgery for EOC at the Mayo Clinic, January 2, 2003, to December 29, 2008

Characteristic	Multivariable HR (95% CI)	P
Past DVT/PE [*]		0.03
Yes	3.14 (1.10–8.97)	
No	Reference	
Smoking history (current/past smoker)		0.01
Yes	2.46 (1.25–4.87)	
No	Reference	
Length of hospitalization	4.29 (1.80–10.23) [†]	0.001

* History of DVT/PE more than 30 days before surgery.

[†] Length of initial hospitalization was evaluated in a univariate Cox regression model as a binary time-dependent covariate that denoted whether the patient was still in the hospital as part of the initial hospitalization.