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Postoperative Thromboembolism in Gynecologic Oncology Patients. Still a Lethal but Preventable Complication

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Abstract

Background: Gynecologic oncology patients are considered high risk for venous thromboembolic events (VTE), which, despite advances in prevention and management, remain a common cause of morbidity and mortality.

Methods and findings: Several clinical trials in gynecologic and general surgery, both for benign and malignant conditions, have addressed the issue of risk assessment and appropriate thromboprophylaxis. This review focuses on epidemiology, risk stratification and preventive measures in patients undergoing surgery for genital tract malignancies. A literature search using PubMed, MEDLINE, and Cochrane search engines was performed using predefined data fields.

Conclusion: Thromboprophylaxis is of utmost importance in this group of patients. Patients' compliance and optimal implementation of the existing available measures could further reduce VTE events in patients with gynecologic malignancies.

Keywords: Thromboembolism; Venous; Deep-Venous Thrombosis; Embolism; Pulmonary; Low Molecular Weight Heparin; Gynecologic Neoplasms

Introduction

Venous thromboembolism (VTE), consisting of deep venous thrombosis (DVT) and pulmonary embolism (PE), represents a major - but preventable - perioperative complication in patients with gynecologic malignancies [1].

Incidence rates vary widely among gynecologic surgical patients, depending on individual and procedure specific factors, presence or absence of cancer, type of cancer as well as the method used for diagnosis. Approximately 14% of those undergoing surgery for benign conditions and 38% of oncological patients without prophylaxis develop VTE [2]. This high burden of thromboembolic events in women with genital tract malignancies is attributed to multiple risk factors such as hypercoagulable state, advanced age, vascular stasis due to pelvic tumor or enlarged lymph nodes, lengthy surgery, prolonged clinostatism and chemotherapy. Even with prophylactic measures the rate of VTE remains as high as 5-18% in this group of patients, while PE risk is 1 - 6.8%, with the higher rates observed in ovarian cancer [3].

While there have been advances in its prevention and management, VTE remains common and often unrecognized cause of morbidity and mortality. PE is the leading cause of postoperative death in gynecologic oncology patients, accounting for 3% of post-surgery deaths. The case – fatality rate for PE in this subgroup is 25%, higher than the 11 -12% observed in non-oncological individuals [4]. Patients developing VTE are also at risk for recurrent VTE and other chronic conditions such as chronic thromboembolic pulmonary hypertension, venous insufficiency, and post thrombotic syndrome (characterized by pain, brownish or reddish skin discoloration, edema and venous ulceration) [1].

Several preventive measures for thromboprophylaxis have been used in abdominal-pelvic surgery, including mechanical (graded compression stockings (GCS), intermittent pneumatic compression (IPC) devices, inferior vena cava (IVC) filters) and/or pharmacologic agents (low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (LDUH), fondaparinux, and low dose aspirin). Periodic surveillance with venous compression ultrasonography (VCU) has also been evaluated [5]. Optimal prophylaxis should take into account and estimate both risk of VTE and bleeding complications from anticoagulation treatment. Although existing models for risk stratification, such as Caprini score, have important limitations, they should be considered as a guide in individualization of management [6]. In those patients, a combination of an aforementioned pharmacologic and a mechanical agent seems to improve preventive efficacy.

Limited data have so far demonstrated that the rate of VTE in patients undergoing laparoscopic surgery is low, even in oncologic patients [7]. However, the necessity of thromboprophylaxis in minimal invasive surgery remains debatable.

Only a few studies of VTE in gynecological cancer surgery have been reported. Considering the high rates of DVT and PE in these patients, we aim to discuss the available literature as regards the risk factors, preventing measures and practice patterns of VTE in female genital tract malignancy surgery. A review of published studies using PubMed, MEDLINE, and Cochrane search engines was performed using predefined data fields.

Epidemiology

The annual incidence of VTE is estimated to be 160 per 100 000 for DVT, 20 per 100 000 for symptomatic non-fatal PE and 50 per 100 000 for fatal autopsy detected PE. The case-fatality rate for PE is 11%, although this percentage is higher in patients with cancer (25%) and lower in young patients [8]. Pharmacological prophylaxis reduces the risk of PE by 75% in general surgical patients and by 57% in medical patients [9].

Trousseau was the first to remark the susceptibility of oncology patients to VTE in 1865. The overall risk of VTE is increased sevenfold in these patients, accounting for 20% of all VTE events. Patients with hematologic malignancies present the highest risk of developing VTE, followed by those with lung and gastrointestinal cancer. Female genital tract oncology patients are also at risk for VTE (adjusted odds ratio (OR), 3, 1 in ovarian and 2, 9 in cervical cancer) [10]. The postoperative rate of DVT was reported to be 38% in this group of patients, while the rate of PE is between 1 to 6.8%, with the highest rates observed in ovarian cancer [2,3]. PE is the leading cause of postoperative mortality in high risk patients with ovarian, cervical and endometrial cancers [11]. In a retrospective cohort study, the mean day postoperatively on which a PE is diagnosed was found to be day 11, while one-year survival rates for patients with and those without PE were 48.0% ± 12% and 77.0% ± 2%, respectively. Two-year survival rates were 36.0% ± 11% and 61.0% ± 3%, respectively [3]. Patients experiencing perioperative thromboembolic event are also at risk for recurrent DVT and chronic post-thrombotic syndrome in approximately 30% of cases while 90% of them suffer milder forms of disability at 2- to 5-year follow-up intervals [12].

The postoperative prevalence of VTE varies depending on the method used for diagnosis. When diagnosed clinically, the prevalence of DVT is 3% and of fatal PE 0.2–0.9%, while by I125 fibrinogen leg scanning performance, the DVT prevalence increases, ranging from 15% to 30%, depending on the risk factors of the individual patient [13]. DVT is usually asymptomatic but can lead to symptomatic PE depending on the clot's location. In a prospective study enrolling 382 females with gynecologic malignancy, 17% of patients developed DVT with the 85% presenting thrombi in the calf veins. Only 4% of these propagated to the proximal leg veins, and an additional 4% became symptomatic pulmonary emboli. 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 [14].

Risk Factors

Gynecologic oncology patients are considered to be high risk population for thromboembolism. The exact mechanism is not completely understood but multiple risk factors can be associated with this phenomenon and thus the overall incidence varies widely depending on the risk factors of the individual patient. Apart from the three factors for the development of thrombi, described by Virchow in 1858, i.e. hypercoagulopathy, venous stasis and endothelial damage, other factors such as prolonged surgery and hospitalization, chemotherapy drugs, advanced age, obesity, hormone therapy, inherited or acquired thrombophilia, presence of a central venous catheter and infection also predispose to VTE [13].

The pathogenesis of the hypercoagulable state of cancer derives from the interplay of multiple variables. Intact tumor cells release procoagulant as well as factors that affect endothelial permeability, which can directly induce thrombin generation. In addition, normal tissues may express procoagulant activity in response to the tumor. Platelet abnormalities and elevated coagulation factors are also implicated. Operative procedures that lead to decreased fibrinolytic activity, underlying thrombophilia, pregnancy, hormone therapy and oral contraceptive use may place a patient into the highest risk category [15].

Reduced mobility associated with cancer and cancer treatment, compression or invasion of blood vessels by an enlarged uterus, pelvic masses, hematomas and lymph cysts can adversely affect blood's drainage, predisposing to venous stasis and the formation of thrombi [16]. Vessel wall injury can either result from coagulation mechanisms and tumor growth, or from surgical procedures.

A prospective study of 411 female patients who underwent major gynecologic surgery without receiving any prophylaxis but from early postoperative ambulation, demonstrated that a history of VTE, presence of malignancy, increasing age, African American race, varicose veins, prolonged surgical duration and prior radiation therapy were independent risk factors for thromboembolism. Pelvic exenteration and radical vulvectomy with inguinal–femoral lymphadenectomy were characterized as high-risk surgical procedures [17]. In a retrospective review of 1862 patients undergoing gynecologic surgery, risk factors associated with the occurrence of thromboemboli included the diagnosis of cancer, history of DVT, hypertension and antihypertensives use, age greater than 60 years and duration of anesthesia more than 3 hours. Patients with two or three of these variables had a 3.2% incidence of developing thromboemboli as compared with a 0.6% incidence of thromboemboli if the patient had none or one risk factor [18].

Limited studies have estimated the rate of VTE in patients with gynecologic cancer undergoing minimally invasive surgery, reporting results lower than 2,4% [7,19,20]and thus implying that this group of patients are at lower risk for postoperative venous thromboembolic events than their open counterparts. These lower rates could be however attributed to the use of some kind of prophylaxis. On the other hand, risk factors for VTE are highly prevalent among patients with gynecologic

malignancies and there are studies reporting that increasing "surgical complexity" (radical hysterectomy, pelvic and paraaortic lymphadenectomy, splenectomy, bowel surgery) might result in higher rates of VTE [19].

On 2012, the American College of Chest Physicians (ACCP) incorporated the Caprini risk assessment model, in order to identify high risk surgical patients for VTE. This risk stratification model, taking into account independent risk factors, determines four levels of risk for VTE that correlate to the incidence of VTE and recommends the prophylactic measures needed for each level. This model is validated in gynecologic oncology patients [6].

Preventive Measures

VTE postoperative occurrence has been shown to decrease by the perioperative implementation of several agents that can be categorized in two groups: mechanical and pharmacologic. The former group includes GCS and IPC devices. These agents reduce venous stasis and favor fibrinolysis. On the other hand, pharmacologic agents including LMWH, LDUH, fondaparinux and low dose aspirin, interfere with the coagulation cascade and inhibit clot formation. Most of these agents have been shown to reduce venous thromboembolism rates.

As aforementioned, calf veins are the most frequent site of postoperative thrombi. As a result foot elevation, early ambulation and GCS may prevent thrombus formation by preventing blood stasis in the calves [17]. Easy implementation and low cost are the the two main advantages of GCS. A randomized controlled trial in a gynecologic surgery population 44, found statistically significant reduction (36%) in the development of DVT in patients wearing GCS. Effectiveness of this measure has been shown to augment when combined with an additional prophylactic agent. In a recent Chinese study, the incidence of VTE in gynecologic oncology patients treated with LMWH plus GCS was significantly lower than that in patients using GCS alone (0.8% Vs. 8.1%, P=0.01) [21].

The inflatable pneumatic sleeve in IPC devices acts in a similar manner to GCS, i.e. compress the calf and thereby reduce venous stasis. The use of IPC device from the beginning of the surgery and for at least five days postoperatively was accompanied by a significant reduction in the incidence of DVT (12.7% IPC group vs. 34.6% control group; P<0.005) in a randomized controlled trial regarding patients undergoing gynecologic surgery [22]. Effectiveness of IPC devises seems to be comparable to that of unfractionated and LMW heparin in major gynecologic operations [23]. Despite these results, compliance seems to be low in clinical practice and efficacy in PE prevention is unproven.

Many controlled trials demonstrated LDUH efficacy in preventing DVT when administered subcutaneously 2 hours before surgery and every 8–12 hours postoperatively [13]. 12-hour interval administration was shown to reduce postoperative DVT in patients undergoing major gynecologic surgery for benign indications in contrast to higher-risk patients with gynecologic cancer [24]. However, 5,000 units of heparin administrated 2 hours preoperatively and every 8 hours postoperatively did provide effective DVT prophylaxis to the latter group [25]. Postoperative bleeding and heparin induced thrombocytopenia, however, usually compromise the use of this agent.

LMWH is demonstrated to effectively prevent thrombosis formation in both benign and malignant surgical cases [26,27]. Longer half-life permits once-daily dosing, while antifactor Xa activity (and less antithrombin activity seen in LDUH) may decrease medical bleeding and wound hematoma formation. Thrombocytopenia presents in lower rates and screening is not needed [28]. However, LMW heparin cost is greater than that of unfractionated heparin. Gynecologic patients undergoing major surgery received equal benefit in prevention of DVT with LMW and LDUH [29]. In cases of renal dysfunction and clearance impairment (GFR<30 ml/min), drug accumulation results in an increased risk of bleeding. Enoxaparin, in contrast to dalteparin and tinzaparin, accumulates rapidly and should be avoided in patients with renal insufficiency [30,31]. The optimal timing to administer LMW heparin was shown to be up to 2 hours preoperatively, for avoidance of major bleeding, or 6 hours postoperatively in hip surgery patients [32]. However there are no randomized trials in gynecologic surgery that address the issue of timing of initiating low-dose unfractionated heparin or LMW heparin. Duration of thromboprophylaxis also remains debatable. Most thromboembolic events occur after hospital discharge and forty percent of oncologic patients develop thrombosis more than 21 days after surgery [33]. Five placebo-controlled trials have investigated the efficacy of prolonged LMW heparin prophylaxis (28 days) in preventing VTE in high-risk patients. In a meta-analysis, incidence of VTE was 6.1% in patients who received prolonged prophylaxis as compared with an incidence of 14.3% in the control group (only hospital prophylaxis) (OR 0.41,95% CI 0.26–0.63; P<0.001), while there was no significant difference in major or minor bleeding between groups [34].

The combined use of two prophylactic methods would potentially further reduce the incidence of venous thromboembolism. Although there are no randomized trials addressing this issue in gynecologic surgery, a retrospective study reported that the lower incidence (1.9%) of VTE in a gynecologic oncology population when IPC and low-dose unfractionated heparin (every 8 hours) or LMW heparin were given in combination as compared to IPC alone (6.5%) [35]. In high-risk gynecologic oncology patients combination of IPC and LMW heparin use seems to be cost-effective [36].

There is no consensus as regards the thromboprophylaxis practice in gynecologic oncology patients undergoing laparoscopic surgery. Until more data are collected, the American College of Obstetricians and Gynecologists (ACOG) recommends administration of pharmacologic thromboprophylaxis similar to that provided to patients undergoing laparotomy- to all patients undergoing surgery, including laparoscopy greater than 30 minutes unless contraindicated due to increased risk of bleeding [37].

Conclusion

VTE remains a major complication in gynecologic oncology surgery. Thromboprophylaxis is of utmost importance in this group of patients, who are considered high-risk and is also warranted in patients who undergo complex laparoscopic surgery. LDUH, LMW heparin, graduated compression stockings, or IPC devices are available preventive measures and dual / prolonged prophylaxis are of additional benefit. However, sub-optimal implementation of available measures in clinical practice and poor compliance still remain an issue waiting to be addressed. A more intense focus on VTE prevention could result in a reduction of morbidity and mortality resulting from thromboembolism in patients with gynecologic malignancies.

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