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Original Research Article

Venous thromboembolism after major gynecological cancer surgery: an analysis of cause and effect from the experience of a tertiary referral oncologic centre

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ABSTRACT

Background: Patients undergoing extensive gynecological oncologic surgeries are at greater risk for developing deep vein thrombosis and pulmonary embolism than other oncological procedures. The anatomical confinement of vessels, lymphatics, and other structures in the restrictive pelvic space is contributory. We aimed to establish the etiopathogenesis of venous thromboembolism (VTE) with our practical experience.
Methods: We present our experience from a tertiary referral oncologic centre in north India in patients with ovarian cancer undergoing cytoreductive surgery (CRS) with or without HIPEC, with a focus on the incidence and etiopathogenesis of deep venous thromboembolism (DVT), including anatomical barriers, restricted movement during surgical dissection, risk stratification and preventive measures.
Results: Of 250 patients who underwent cytoreductive surgery (CRS) for ovarian cancer, 124 additionally underwent hyperthermic intraperitoneal chemotherapy (HIPEC). 20 (8%) patients were diagnosed with DVT within 30 days of surgery, and 3 (1.2%) were detected after 30 days. It is the most common significant postoperative morbidity.
Conclusions: DVT is the most common postoperative complication in patients undergoing CRS+HIPEC for carcinoma ovary. Anatomical confinement, closed dependant spaces and more significant surgical trauma to pelvic vessels and lymphatics may be the leading cause. Detailed knowledge of anatomy and careful surgical dissection may prevent the development of DVT.

Keywords: Deep vein thrombosis, DVT prevention, Surgery gynecological malignancies, Venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a significant complication after gynecological oncology surgery with an incidence of 15.6%.[1] Despite significant improvement in surgical techniques and perioperative prophylaxis, it remains a major cause of morbidity and mortality. The incidence of VTE is likely underestimated as it is sometimes asymptomatic.[2]

Patients with gynecological cancers are at higher risk of developing VTE. The risk of VTE is 4 to 7 times higher in cancer patients than in the general population, with approximately 20% of cancer patients having VTE.[3] The Million Women Study showed that the risk of VTE at 12 weeks postoperatively after oncologic surgery was 1/85 and 1/365 for benign gynecologic surgery.[4]

The risk of VTE is the highest in ovarian cancer among all gynecological malignancies and one of the highest among all solid tumours.[5] DVT has been observed in up to 38% of gynecologic oncology patients postoperatively.[6] Pulmonary embolism rates range from 1% to 26% in different studies and account for 3% of all deaths after gynecologic surgery, which makes it the leading cause of postoperative death in patients with gynecological malignancies.[7]

In the present study, we share our experience from a tertiary care oncology institute regarding the incidence of deep venous thrombosis incidence and its mortality and morbidity in carcinoma ovary patients.

METHODS

In this study, 250 consecutive patients with ovarian cancer who underwent cytoreductive surgery in the department of surgical oncology at All India Institute of Medical Sciences, New Delhi, between 2014 and 2019 were evaluated. Postoperative complications (Calvien-Dindo score III, IV) were noted under two categories: i) early: within 30 days, and ii) late: 31-90 days.

DVT was suspected when there was lower limb pain, poor performance status or a history of VTE preoperatively. For patients with symptomatic DVT or clinical suspicion, Doppler Ultrasonography of bilateral lower limbs was performed using a 3- to 7.5-MHz transducer, assessing the iliac, femoral, great saphenous, popliteal, peroneal, posterior tibial and soleal veins. The iliac and femoral veins were evaluated in the supine position, while all the other veins were assessed in an upright position. All veins were imaged on both transverse and long-axial views. Venous lumina was examined by manual compression with the transducer and colour Doppler imaging. Valsalva manoeuvre was performed to see the reaction of intrapelvic veins- no increase in the venous diameter in response to deep inspiration or Valsalva was suspected to represent proximal venous flow disturbance. Our protocol was to preoperatively evaluate all ovarian cancer patients with comprehensive imaging studies using enhanced abdominal and pelvic CT to detect metastatic tumours and a thrombus in the iliac veins or the inferior vena cava. These patients were monitored in the postoperative period again for DVT. If DVT was discovered through venous Ultrasound Imaging or contrast-enhanced CT, the patient was further investigated for the presence of PE.

Other postoperative complications were also noted and presented in tables later in the article.

RESULTS

Our centre has performed 454 surgeries for various gynecological malignancies during the study period. We have included patients with ovarian cancer as they represent the largest group- 250 cases of carcinoma ovary underwent cytoreductive surgery. The mean age at presentation was 48.28 years (range 19 to 80 years). Among these, 32 patients were 35 years or younger. Of the 250 patients, 212 (84.8%) were symptomatic at presentation. The remaining patients were diagnosed with ovarian cancer incidentally when imaging studies were performed for other complaints. Among 250 patients, 112 (44.8%) received neoadjuvant chemotherapy, and 62 (24.8%) had an upfront cytoreductive surgery. Seventy-six cases (30.4%) were recurrent carcinoma ovary. 124 (49.6%) patients who received HIPEC post-cytoreduction performed with cisplatin for 60 minutes with the semi-open method.

Table 1: Post operative complications.

	Primary CRS	Interval CRS	Secondary CRS
Early 16.4%	13/62 (20.9%)	16/112 (14.2%)	12/76 (15.7%)
Late 4.8%	3/62 (4.8%)	5/112 (4.4%)	4/76 (5.2%)

Table 2: Early complications (within 30 days).

	No. of patients	Percentage
DVT	20	8
Paralytic ileus	8	3.2
Acute kidney injury (Derangement of KFT)	8	3.2
Re-exploration (any cause)	7	2.8
Surgical site infection	6	2.4
Pain abdomen	6	2.4
Intraabdominal collection	4	1.6
Bladder injury	4	1.6
Burst abdomen	3	1.2
Enterocutaneous fistula	3	1.2
Chyle leak	2	0.8
Lymphocele	2	0.8
Ureteric injury	1	0.4
Subclavian thrombosis	1	0.4
Bile leak	1	0.4

Out of 250 operated patients, 41 (16.4%) and 12 (4.7%) patients had early and late complications, respectively (Table 1). The details of these early complications are tabulated in Table 2.

Table 3: Late complications (31-90 days post-operatively).

	No. of patients	Percentage
Lymphocele	4	1.6
DVT	3	1.2
SAIO	3	1.2
Incisional hernia	2	0.8
Ureteric stricture	2	0.8
Enterocutaneous fistula	2	0.8
Ascites (non-malignant)	1	0.4

Deep vein thrombosis (8%) was the most common early complication among the patients undergoing cytoreductive surgery (with or without HIPEC) for carcinoma ovary. DVT was found in 7 (5.55%) patients who underwent cytoreductive surgery and 13 (10.4%) patients undergoing cytoreduction surgery, followed by HIPEC. It also was the

second most common late complication, lymphocele being the most common (Table 3).

Four (1.6%) patients died within 6 hours after surgery from pulmonary embolism, which the authors describe as a 'bowled out phenomenon', a fatal and unexplained complication after CRS+HIPEC, appearing as a bolt from the blue.[8]

DISCUSSION

Trousseau first reported an association between DVT and malignancy in 1865.[8] In 1858, Virchow postulated that three factors, i.e., hypercoagulability, venous stasis, and vessel wall injury (endothelial damage), were responsible for forming thromboembolism.[9]

Patients with gynecological malignancy have multiple risk factors predisposing them to thromboembolic events in addition to the presence of active malignancy. These include advanced age; high body mass index (BMI); medical comorbidities, immobility; hormonal therapy, a history of oral contraceptive use or tamoxifen intake; venous obstruction by a pelvic mass, thrombin formation and the effect of therapy (e.g., prolonged operative time, chemotherapy, and targeted therapy).[10]

Commonly used chemotherapeutic agents in gynecological malignancy in the neoadjuvant and adjuvant settings, such as platinum-based regimens and bevacizumab, have also been associated with higher rates of VTE, raising the risk by two-to-six-fold.[11]

Ovarian malignancy usually presents with a large tumour in the pelvis and a significant volume of ascites, which compress the main pelvic blood vessels, leading to venous stasis and an increase in the risk of subsequent DVT. Invasion of tumours into the parametria, the pelvic wall and its structures in cervical and endometrial cancers can cause vascular endothelial damage, promoting clot formation in vessels.

Thrombocytosis is often seen with gynecological tumours, as they express procoagulants (e.g., tissue factor and cancer procoagulant) and glycoproteins, encouraging platelet adhesion. Factors affecting endothelial permeability (e.g., vascular endothelial growth factor, TNF alpha, interleukins) and fibrinolytic pathway are also expressed in gynecological tumours, increasing the thrombotic risk .[12]

Lymphovascular anatomy and surgical factors

Many surgical and anatomical factors alter the three factors described by Virchow, thereby promoting the development of DVT.

Pelvic veins have thin walls, which may be easily injured during pelvic surgeries. The presence of numerous collaterals between the veins of the rectum, bladder and within the reproductive system makes it a low-pressure venous system, which further results in pelvic venous congestion and slowing of blood flow in the region, making pelvic surgeries more prone to the development of thromboembolism.

The proximity of vessels to the tumour due to the confined space within the bony walls of the pelvis leads to venous stasis.

Due to the tumour and nodal burden in the pelvis, neovascularisation creates a thin-walled vessel plexus, which prone to be injury during the dissection of the tumour and lymph nodes. These injuries can lead to thrombus formation, as these vessels are directly related to pelvic main vessels.

Surgery for gynecological malignancies is usually extensive and prolonged. The patient occupies a fixed supine or lithotomy position for a lengthy period, which promotes venous stasis in pelvic vessels, as the pelvis is the most dependent part of the body. Moreover, anaesthetic drugs may cause venous distension, aggravating the sluggish blood flow in pelvic vessels, thus increasing the risk of VTE.

Direct injury to the vessel wall may occur during cytoreductive surgeries and lymph node dissections, leading to coagulation pathway activation and clot formation.

Embryologically, pelvic lymphatics arise from the pelvic veins. Thereby, there can be venous trauma, developing DVT during the dissection of lymph nodes.

Hematomas, or lymphoceles, may form following surgery, leading to postoperative venous stasis by compressing the pelvic vessels.

Women with gynecologic cancers often have advanced age, high BMI or other comorbidities and chemotherapy-induced fatigue, which compound perioperative immobility and contribute to the formation of DVT.

Risk assessment and preventive measures

Patients with gynecological malignancies undergoing surgery must have a proper assessment of the postoperative risk of VTE. The American College of Chest Physicians (ACCP) recommends various risk assessment tools, like the Caprini and Rogers scores, to determine the VTE risk level.[13]

The Caprini score has been validated in patients with gynecological malignancies (Table 4).[14] The score was calculated by adding scores allotted to individual risk factors, given below:

Score 0-1: low risk, score 2: moderate risk, score 3-4: high risk, score ≥ 5: highest risk.

Table 4: Caprini risk assessment model.

Each risk factor =1 point	Each risk factor =2 points	Each risk factor =3 points	Each risk factor =5 points
• Age 40-59 years • Minor surgery planned • BMI >30 kg/m^2 • History of prior major surgery (<1 month) • Swollen legs (current) • Varicose veins • Sepsis (<1 month) • Abnormal pulmonary function (COPD) • Acute myocardial infarction (<1 month) • Congestive heart failure (1 month) • History of IBD • Medical patient currently at bed rest For women only: • Pregnant of post-partum • History of unexplained or recurrent spontaneous abortion • Oral contraceptives or hormone replacement therapy	• Age 60-74 years • Arthroscopic surgery • Major open surgery (>45 minutes) • Laparoscopic surgery (>45 minutes) • Prior cancer (except non-melanoma skin cancer) • Present cancer (except breast and thyroid) • Confined to bed (>72 hours) • Immobilizing plaster cast • Central venous access	• Age >75 years • History of VTE • Family history of VTE • Present chemotherapy • Positive factor V Leiden • Positive Prothrombin 20210A • Positive Lupus anticoagulant • Elevated anticardiolipin antibodies • Elevated serum homocysteine • HIT • Other congenital or acquired thrombophilia	• Major surgery lasting >6 hours • Stroke (<1 month) • Elective major lower extremity arthroplasty • Hip, pelvis, leg fracture (<1 month • Acute spinal cord fracture or paralysis (<1 month) • Multiple traumas (<1 month

However, it must be remembered that patients with most patients with gynecologic cancer undergoing open surgery will have a minimum Caprini score of >4 (i.e., high risk). A retrospective study found that among 1,123 patients with gynecologic cancer undergoing laparotomy over seven years and using the score as a predictor of venous thromboembolism, 92% had a Caprini score of >4 (i.e., highest risk). However, the incidence of venous thromboembolism among this population was 3.3%.[14] Another series of 17,713 patients with gynecologic malignancies from a national quality database reported that 97% were at the highest risk.[15] Hence, a uniform pre- and postoperative anticoagulation policy may be adopted in managing gynecological cancer.

After the high incidence of postoperative DVT was noted, the Department implemented specific changes in the patient management protocol based on various guidelines. These included the initiation of pharmacologic prophylaxis 12 hours prior to planned CRS and 6 hours after the completion of surgery. Pharmacologic and mechanical prophylaxis were continued for at least two weeks after surgery.

Prophylactic methods have significantly reduced the incidence of VTE after major surgery. Various methods are available for prophylaxis of VTE after surgery for gynecological malignancies, which should be inexpensive, practical, have no significant side effects, be well accepted by the patient and nursing staff, and be widely applicable to most patients.

Broadly, VTE prophylaxis methods may be divided into mechanical and pharmacological measures.

Mechanical methods

Long surgical duration and postoperative immobilisation lead to venous stasis, especially in the veins of calf muscles. Early ambulation, foot end elevation and adequate hydration are encouraged to prevent stasis.

Graduated compression stocking

Well-fitted stockings have shown a modest benefit in preventing VTE.[16] It is simple to use, low cost and without any significant side effects and is often used in the routine postoperative periods.

Intermittent pneumatic compression (IPC) devices

Reduce stasis by intermittently compressing the calf with a sleeve inflated to 50 mmHg by a pneumatic pump. This increases venous flow and results in a pulsatile emptying of the calf veins. It augments endogenous fibrinolysis, resulting in thrombus lysis early before they become clinically significant.[17] When used intraoperatively and in the postoperative period, IPC devices have comparable effectiveness to LMWH in preventing DVT.[18] Intermittent pneumatic leg compression is more cost-effective than pharmacologic methods and has no significant side effects or risks. Moreover, they constitute the primary prophylaxis immediately after surgery when anticoagulants cannot be initiated. However, the continued use of IPC devices after

commencing pharmacologic anticoagulants does not provide an additional benefit, and they have the disadvantage of limiting mobility.

Early mobilisation

It naturally prevents venous stasis, thereby preventing DVT.

Pharmacologic methods

VTE prophylaxis is recommended in all admitted medical or surgical patients with cancer as ambulation after hospital admission is limited, increasing the VTE risk. Low-dose heparin prevents VTE and its associated mortality in major benign and oncologic surgery.[19] The available anticoagulants for patients undergoing gynecologic oncologic surgery include Unfractionated heparin, low-molecule heparin, fondaparinux, and apixaban.

Low molecular weight heparin (LMWH)

It is fragments of heparin that range from the size of 4,500 to 6,500 Da. They have more anti-Xa and less antithrombin activity than unfractionated heparin, leading to fewer bleeding complications and wound hematoma formations.[20] However, the cost is greater than that of heparin. It has a half-life more than that of heparin, allowing once-a-day dosing.

Unfractionated heparin (UFH)

It is the most widely studied pharmacologic method for preventing DVT. When used in the dose of 5,000 units administrated 2 hours preoperatively, and every 8 hours postoperatively, it showed significant effectiveness in preventing DVT in patients with gynecological malignancies.[21] However, the slightly higher risk of bleeding and heparin-induced thrombocytopenia has compromised its use.

Fondaparinux

It is an indirect inhibitor of activated factor Xa, which potentiates antithrombin. It was found to be as efficacious as LMWH in the prevention of postoperative VTE in a double-blinded randomised trial of 2048 patients undergoing major abdominal surgery, with comparable rates of significant bleeding during surgery (2.3-3.4%).[22]

Apixaban

It is an oral factor Xa antagonist, has been approved for prophylaxis in gynecologic cancers. A trial on 500 women with gynecological cancers randomised to receive 28 days of oral apixaban 2.5 mg twice daily or subcutaneous enoxaparin 40 mg once daily post-surgery had comparable rates of VTE, bleeding events and adverse effects. Patient satisfaction was significantly greater in the apixaban group. Oral anticoagulants circumvent many side effects of using LMW or unfractionated heparin, i.e., injection site pain and cost.

As mentioned earlier, The Caprini risk score recommends different prophylactic regimens based on an individual patient's risk score (ACCP guidelines).[13] In low-risk patients: Graded compression stockings or intermittent pneumatic compression. In moderate-risk patients: Intermittent pneumatic compression, low-dose heparin, or low molecular weight heparin. In high-risk patients: Intermittent pneumatic compression and low-dose heparin or low-molecular-weight heparin. Consider prolonged prophylaxis for 28 days with LMWH, which has been shown to significantly reduce the incidence of VTE in patients undergoing open abdominal surgeries for malignancies.[24] NCCN recommends extended prophylaxis for high-risk patients for 28 days (4 weeks).[25]

The initiation of prophylactic measures preoperatively in patients undergoing surgery for gynecological malignancies has shown a decreased rate of DVT and its associated deaths.[26]

ERAS society recommendation on venous thromboembolism prophylaxis in gynecologic/oncology patients[27]

Patients at increased risk of VTE should receive dual mechanical prophylaxis and chemoprophylaxis with either low molecular weight heparin or unfractionated heparin.

Prophylaxis should be initiated preoperatively and continued postoperatively.

Extended chemoprophylaxis (28 days post-op) should be prescribed to patients with high-risk ACCP criteria, including patients with advanced ovarian cancer.

Highlights

Pelvic surgery, especially major gynecological procedures, is prone to develop DVT compared to surgery in other sites.

The anatomical distribution of vessels and its relation to tumours in a confined space causes venous stasis, among other surgical factors and thrombogenic protein expression.

Tumour, lymph nodal disease burden, and forced trauma induced by extensive surgery may lead to DVT.

Prophylaxis for DVT starting 12 hours prior and 6 hours after surgery for a minimum of 2 weeks is advisable to avoid these highly morbid complications.

Prehabilitation, mechanical prophylaxis, and early mobilisation are of vital concern to prevent the development of VTE.

CONCLUSION

VTE is a significant complication and an important cause of morbidity and mortality in patients undergoing major gynecologic oncological surgeries like those for carcinoma ovaries in our cohort of patients. Anatomical confinement of lymphovascular structure within the closed space and other factors is more prone to develop VTE.

Details of anatomical knowledge of pelvic structure, fine dissection, thromboprophylaxis, and early mobilisation may reduce this deadly complication.

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