



Update on extended prophylaxis for venous thromboembolism following surgery for gynaecological cancers



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ABSTRACT

Gynaecological cancers are associated with high rates of VTE varying from 6% in endometrial cancer to up to 43% in clear cell cancer of the ovary. The risk of VTE is particularly high following gynaecological cancer surgery where VTE occurs in 6–7% of patients despite LMWH prophylaxis. The presence of a gynaecological malignancy increases the rate of post-operative VTE fourfold compared with patients with benign disease. The risk of VTE persists beyond hospital stay hence guidelines recommend extended prophylaxis (28 days) with LMWH for patients undergoing pelvic abdominal surgery for cancer. Gynaecological cancer surgery has evolved with increasing use of Minimally Invasive Surgery (MIS) and improvements in post-operative care with associated shorter hospital stay. The aim of this review is to evaluate on the risk of venous thromboembolism following gynaecological cancer surgery and the role of extended thromboprophylaxis in the era of MIS. The risk of VTE following MIS for cancer is low and more data is required to justify the use of extended prophylaxis. VTE risk varies depending on tumour, patient, and treatment factors. Individual risk assessment is required to optimise prophylaxis in these patients. Barriers to the use of extended prophylaxis include concerns regarding bleeding risk and physician perception that the risk of VTE is low particularly following laparoscopy. The introduction of new oral anticoagulants may play a role in post-operative prophylaxis in the future however data is lacking in gynaecological cancer patients.

1. Introduction

Venous thromboembolism (VTE) is a life-threatening event and is the leading cause of death in cancer patients after the cancer itself. It is the most common cause of death in cancer patients in the first 30 days post cancer surgery [1]. VTE occurs in 117/100,000 patients annually in the general population; this risk is four times higher in cancer patients and seven times higher if they are receiving chemotherapy [2,3]. Rates of VTE in cancer patients range from 0.5–20% per annum and 5–10% of all cancer patients develop VTE during the first year after diagnosis [4]. This risk varies between different sites of cancer. Pancreatic cancer has one of the highest rates of VTE with rates as high as 25% [5]. Lung cancer is associated with a VTE rate of 3% within the first 2 years of diagnosis [6]. Rates in the most common types of ovarian cancer are reported to be between 9–11%, this risk is higher in clear cell cancer of the ovary where rates of 43% have been reported [7,8].

In addition to the cancer itself, other factors also contribute to the risk

of VTE, these include patient related factors such as advanced age, ethnic background, gender and medical comorbidities and cancer related factors; site, stage, and type of cancer [9]. Metastatic disease significantly increases the risk of VTE as 56% of cancer related VTE occurs in those with metastatic disease [10,11]. Asian women with endometrial cancer, have a lower VTE risk, while Hispanic women carry the highest risk [12]. Treatment factors such as chemotherapy, hormonal treatment and surgery all increase VTE risk [12,13].

All gynaecological cancer patients, like other cancer patients, are at high risk of VTE however, ovarian cancer holds the highest risk [4,8,14,15]. This is due in part to the location of the tumour in the pelvis and massive ascites compressing the major blood vessels as well as procoagulant material emanating from the tumour [16]. Lack of a screening tool for ovarian cancer results in late presentation; more than 80% of women with ovarian cancer present with metastatic disease which contributes to the increased risk of VTE. The risk of VTE in endometrial cancer patients is estimated as 6% in the 2 years following diagnosis [14]. However the

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incidence of endometrial cancer is increasing, which is explained in part by the global epidemic of obesity, a risk factor for the disease and a contributor to the disease pathophysiology [12,17]. Obesity is also an independent risk factor for thrombosis in gynaecological cancer [13]. Additional risk factors for VTE in endometrial cancer include histology, surgical complexity, and advanced cancer stage [11,14]. In contrast to ovarian cancer, endometrial cancer patients present early and frequently undergo laparoscopic surgery which may contribute to the lower VTE rate. The exception to this is uterine sarcoma, a more aggressive tumour type than other endometrial cancers, which is associated with a higher risk of VTE compared with other endometrial cancers [18].

Data is lacking on VTE risk in cervical cancer patients and the reported risk varies from 0-34%; this wide range is attributed to the heterogeneity of the studied population [14]. It is also thought that VTE in cervical cancer maybe under reported [19]. Though the incidence of cervical cancer is declining due to efficient screening programmes in most developed countries, cervical cancer remains a significant burden in the developing countries due to lack of screening facilities and trained personnel [20].

1.1. Pathogenesis of VTE in gynaecological cancer (Fig. 1)

Virchow first described the pathogenesis of cancer related VTE as a triad containing three main factors contributing to cancer associated thrombosis: activation of haemostasis, venous stasis and endothelial injury [21]. Large gynaecological tumours in the pelvis and the presence of ascites can compress pelvic veins causing venous stasis and thrombus formation [22]. In cervical cancer, tumour invasion of the parametria and pelvic wall can cause endothelial damage and activation of endothelial cells [14]. Endothelial cell damage also results from chemotherapy treatment which we have shown can down-regulate the activation of protein C resulting in a loss of the thromboresistant phenotype of these cells [23]. Our group and others have demonstrated that ovarian tumours in particular, express procoagulant genes including Tissue Factor which trigger coagulation activation [24,25]. Activated platelets are a key factor in the survival of circulating tumour cells in ovarian cancer and contribute to the increased procoagulant activity observed in these patients [26]. Cancer is frequently considered as a pro-inflammatory state. Gynaecological tumours also express cytokines and adhesion molecules which facilitate increased coagulation activation and have been linked to venous thrombosis risk in cancer [22]. Obesity which is common in endometrial cancer has been associated with a state of low-grade systemic inflammation characterized by an adipose tissue driven acute-phase response resulting in secretion of cytokines such as IL-6, IL-1, IL-8, and tumour necrosis factor (TNF), all of which contribute to thrombus formation [27] (Fig. 1).

The combined activation of these pathways results in a prothrombotic state which is particularly pronounced in gynaecological cancers and is further exacerbated by surgery and the resulting immobility of the patient in the immediate post operative period.

1.2. Surgery in gynaecological cancer

Surgery remains the cornerstone of treatment in gynaecological cancer patients. The aim of surgery is to achieve full staging of the cancer and to obtain an optimal surgical debulking of the tumour. This may involve a multiorgan surgery, hysterectomy, salpingo-oophorectomy, pelvic and para aortic lymph node dissection in addition to bowel resection. In cases of ovarian cancer, more than one third of patients will have an upper abdomen procedure such as splenectomy, partial gastrectomy or liver mobilization [28]. This extensive surgical approach increases the risk of post-operative VTE and it is not surprising therefore that VTE is the leading cause of mortality in these patients in the post-operative period [29]. In ovarian cancer, one in every seven women undergoing debulking surgery developed VTE postoperatively [1]. In ovarian cancer patients, it is estimated that 14% of in hospital mortality is

Pathogenesis of Venous Thromboembolism in Gynaecological cancers

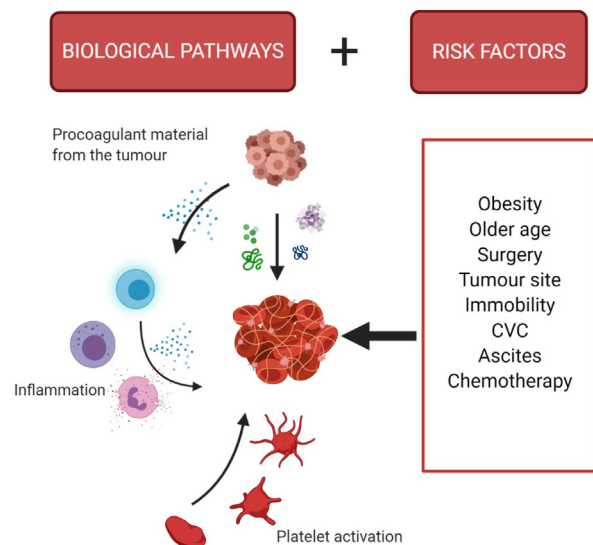


Fig. 1. Pathogenesis of Venous thromboembolism in gynaecological cancers.

due to pulmonary embolism (PE) and 8.3% occurs within 30 days of surgery [30].

Minimal invasive surgery (MIS) is gaining popularity among gynaecology surgeons over open laparotomy for selected patients. MIS can be either laparoscopy or robotic surgery. Laparoscopies use a two-dimensional camera and small fine instruments to operate. Though robotic surgery availability is limited in some centres due to financial issues, it guarantees better visibility and surgical accessibility which is an extra advantage in patients with high body mass index (BMI) [31]. Patient selection criteria determining the surgical approach include the stage of the cancer and the complexity of the procedure. Open laparotomy is necessary for advanced ovarian cancers which require optimal debulking and allow the delivery of intact ovarian cyst or mass, avoiding upstaging of the tumour. Laparoscopy is more appropriate in cases of endometrial cancer and robotic surgery has a major role in advanced endometrial cancer and in patients with high BMI [32]. A meta-analysis of data from eight randomised controlled trials (RCTs) conducted by Zullo et al., showed a similar intraoperative complication rate between laparoscopy and laparotomy (RR 1.25; 95% CI: 0.99–1.56) [33]. Less blood loss occurred compared with laparotomy however, operative time was longer with laparoscopy. There were no significant adverse effects of a laparoscopic approach on the overall survival, disease-free interval or cancer-related survival in the study (OR 0.96, 0.95 and 0.91, respectively) [33]. The ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer [34] recommend MIS for low and intermediate risk endometrial cancer and they advise that MIS should be considered for high risk endometrial cancer.

MIS was the standard treatment for cervical cancer, however publication of a randomised trial altered practice patterns [35,36]. The Laparoscopic Approach to Cervical Cancer trial (LACC) randomly assigned cervical cancer patients to open laparotomy or MIS (either laparoscopy or robotic surgery). The trial was put on hold due to imbalance in deaths, between the two randomised arms. After analysis of the data it was confirmed that disease-free interval was reduced following minimal invasive radical hysterectomy compared to open laparotomy. MIS was associated with a lower rate of overall survival (3-year rate, 93.8% vs. 99.0%; hazard ratio for death from any cause, 6.00; 95% CI, 1.77 to 20.30). This finding resulted in a return to open surgery as the recommended surgical approach for cervical cancer.

1.3. Gynaecological cancer surgery and VTE

Surgical complexity is an independent risk factor for post-operative VTE in gynaecological cancer patients [7,37,38]. Ovarian cancer surgery has the highest risk of VTE among all gynaecology cancer types, carrying 1.5 times higher risk compared to other gynaecological cancer types [37]. Most postoperative VTE cases occur after the first post-operative week [30]. Pulmonary embolism is significantly increased following cancer surgery compared with patients with benign disease. In a large database of 1,373 surgical patients undergoing major abdominal surgery of which 507 had a diagnosis of cancer, the incidence of pulmonary embolism among cancer patients was 4.1% compared with 0.3% with patients with benign disease, mechanical thromboprophylaxis was the sole thromboprophylactic method used in this study [39].

The risk of post-operative VTE in cancer patients persists after hospital discharge. Among gynaecological cancer patients who develop VTE post operatively, 40% will do so more than 21 days after surgery [40,41]. Among endometrial cancer patients diagnosed with VTE, 73% of VTE patients who underwent MIS and 43% of VTE patients who had open surgery were diagnosed with a VTE after hospital discharge [41]. International clinical practice guidelines recommend pharmacological thromboprophylaxis to start 2–12 hrs preoperatively and continue for at least 4 weeks in high risk cancer patients [42]. Some centres recommend using thromboprophylaxis for up to 3 months depending on the individual risk factors [43].

MIS significantly reduces the risk of VTE by one third compared to open surgery [41]. This reduction is attributed to early mobility, reduced hospital stay & less intraoperative blood loss. Hospital stay is an established risk factor for VTE, Herner et al showed that each additional day of hospital stay increases the VTE risk in the general population by 17% [44]. Intraoperative blood loss resulting in blood transfusion is another known risk factor for VTE [45].

1.4. Prediction of VTE in gynaecological cancer

Risk models have been suggested as a method to predict the risk of VTE and identify high risk patients for appropriate thromboprophylaxis. The recommended risk assessment method for surgical patients is the Caprini risk score however, when this is used in gynaecologic cancer surgery, >90% of patients are assessed as high risk even though only a small proportion of these developed VTE [46,47]. The Khorana score is a risk model based on easily available clinical variables and was developed for patients receiving chemotherapy [48]. Although the Khorana score has been extensively validated, it is more useful in mixed populations of cancer patients as it is heavily dependent on tumour site. As the Khorana score places all patients with gynaecological cancer in the intermediate-risk category, it is of limited use in this population and is not useful for identifying lower-risk patients [13]. The Roger score is a multivariate scoring system developed for surgical & vascular patients [49]. In a large study of gynaecological cancer patients, the Caprini and Roger risk scores were used to assess postoperative VTE risk in the first 30 days post surgery [41]. The study concluded that all gynaecological cancer patients scored as extremely high risk on the Caprini risk score (97%) and on the Roger risk score (63%), limiting the ability of the user to discriminate relative VTE risk [41]. In addition, surgical approach was not accounted for in either method of VTE risk assessment. Based on those recommendations a need for a specific scoring system for gynaecological cancers arose. The Thrombogyn score is a risk model which is specific for gynaecological cancer patients and can identify gynaecological cancer patients at high risk and low risk of VTE post-surgery, extension of the score with blood biomarkers improves the predictive ability of the score [13].

1.5. Thromboprophylaxis in gynaecological cancer patients post-surgery

Thromboprophylaxis can be mechanical (e.g. intermittent pneumatic

compression) or pharmacological or a combination of both. Prophylaxis with Low Molecular Weight Heparin (LMWH) reduces the risk of VTE post surgery [50]. Dual postoperative thromboprophylaxis post laparotomy (using pneumatic compression and LMWH) is efficient in reducing VTE particularly in high risk patients [51]. Due to the well-recognised high rate of VTE in cancer patients post-surgery, The American Society of Clinical Oncology and the American College of Obstetrics and Gynaecology recommends using thromboprophylaxis for cancer patients undergoing surgical intervention starting prior to surgery and for at least 7–10 days and to consider extended prophylaxis in high risk patients [52, 53]. Several studies have shown that extended prophylaxis in patients undergoing open cytoreductive surgery for cancer reduces the incidence of VTE post operatively [1]. However, the data with regard to MIS is controversial with some studies questioning the rationale for extended prophylaxis given the low VTE rate following MIS [54].

In a meta-analysis of patients undergoing pelvic-abdominal surgery for cancer, Carrier et al showed that, extended thromboprophylaxis (28–30days) was superior to standard thromboprophylaxis (6–10 days) in reducing postoperative VTE risk without additional bleeding risk [50]. The rationale for the guidelines was based on randomised clinical trials comparing standard in hospital prophylaxis with extended 28-day prophylaxis. The ENOXACAN II trial [55] was a double-blind study of 332 patients undergoing open abdominal or pelvic cancer surgery, patients received enoxaparin for 6–10 days and were randomised to enoxaparin or placebo for a further 21 days. Screening venograms were done on day 25–30 or sooner if patients showed symptoms (Table 1). The use of extended prophylaxis reduced the risk of VTE from 12% to 4.8% without any significant increase in bleeding, this reduction was sustained at 90 days post-surgery. The FAME trial concluded that dalteparin for 28 days is more efficient in reducing the VTE rate than a 7-day course in patients undergoing open surgery with 590 patients recruited in a double blind-randomised clinical trial [56] (Table 1).

The CANBESURE trial was a double-blind study which enrolled 626 patients undergoing abdominal or pelvic cancer surgery [57] (Table 1). Patients received 3500 IU of bemiparin subcutaneously once daily for 8 days and were then randomized to receive either bemiparin or placebo for 20 more days. Bilateral venography was performed after 20 days. 4.6% of patients in the bemiparin cohort suffered a VTE compared with 0.8% in placebo cohort. The study showed that bemiparin for 4 weeks resulted in a non significant reduction in the composite outcome of VTE and death without increased major bleeding. Proximal DVT was significantly reduced in the extended prophylaxis arm. In a meta-analysis, all three randomised trials show high rates of VTE which were substantially reduced by extended prophylaxis [58].

Despite these reassuring reports, observational studies of gynaecological cancer patients have not shown such definitive results and rates of VTE post-surgery are generally lower than those reported in randomised trials [59] (Table 2). In contrast to observational studies, randomised trials incorporate screening venograms which can detect asymptomatic VTE. A recent screening study of gynaecological cancer patients showed higher rates of VTE (7.3% of patients with cervical cancer, 11.5% of those with endometrial cancer and 27.0% of those with ovarian cancer) than have been reported in observational studies suggesting a high rate of asymptomatic VTE in gynaecological cancer patients [60].

Several observational studies have evaluated the efficacy of extended thromboprophylaxis in gynaecological cancer post-surgery. Schmeler et al. reported that although VTE was reduced in patients receiving extended prophylaxis at 30 days, no effect was observed at 90 days post-surgery [61] (Table 2). The time to VTE was increased in the extended prophylaxis group which suggested that extended prophylaxis delayed rather than prevented VTE. In a similar observational study, Marques de Marino et al reported no benefit of 28 days extended prophylaxis in comparison to a 7-day course in terms of reducing VTE incidence in gynaecological cancer patients post-surgery [62]. In contrast, the introduction of preoperative thromboprophylaxis (at induction of anaesthesia) followed by 14 days LMWH prophylaxis in patients undergoing

Table 1

Randomised controlled trials of extended prophylaxis post surgery in cancer patients. DVT= Deep Vein Thrombosis. PE = Pulmonary Embolism. LMWH = Low molecular weight heparin. RRR = relative risk reduction. VTE = Venous Thromboembolism. OD = Once daily.

Study	Study design	Surgical approach	Primary Efficacy outcome	Patients (n)	Gynae-Oncology Patients (n)	Extended prophylaxis Regimen	VTE screening	VTE Risk reduction % [95%CI]	Conclusion
ENOXACAN II Bergqvist et al. (2002) [55]	Randomised placebo based double blind trial	Open	Asymptomatic and symptomatic DVT or PE occurring during the double blind period	332	28	Enoxaparin (40 mg) OD for 31 days v placebo from day 8 to 31 days post surgery	Venography day 25–31	VTE RRR=60% [10–82%] P=0.02	<ul style="list-style-type: none"> • Enoxaparin (4 weeks) reduces VTE post surgery • No increased risk of bleeding.
FAME Rasmussen et al.(2006) [56]	Assessor-blinded, open-label, randomized trial	Open	Asymptomatic and symptomatic DVT or PE day 7–28 days post surgery	590	60	Dalteparin (5000 IU) OD for 28 days vs 7 days post-operative	Venography day 28	VTE RRR= 55% [15–76%] P=0.012	<ul style="list-style-type: none"> • Extended prophylaxis Dalteparin reduces the rate of VTE • No increased risk of bleeding
CANBESURE Kakkur et al. (2010) [57]	Randomized, placebo based double-blind study	Open	symptomatic and asymptomatic DVT, non-fatal PE and all-cause mortality	626	71	Bemiparin 3500 IU for 6–10 days Bemiparin Vs placebo 28 days post-surgery	Venography after 20 days	VTE and Death RRR=24.4% [-23.7–53.8%] (P = 0.26) Proximal DVT RRR 87.9 [4.0–98.5%] (P<0.02)	<ul style="list-style-type: none"> • Decrease in proximal DVT only • Non significant reduction in VTE and death
Vedovati et al. (2014) [81]	Randomized controlled study	laparoscopic	symptomatic VTE (DVT or PE ultrasonography at day 28 ± 2 from surgery	255	0	LMWH (dalteparin/ enoxaparin for 28 days	Venography at day 28 ± 2 Extended prophylaxis patients only	VTE at 4 wks extended treatment arm = [0–3.3%] (P= 0.001)	<ul style="list-style-type: none"> • Significant reduction in VTE events

Table 2

Observational studies of the effect of extended prophylaxis post surgery in gynaecological cancer patients. DVT= Deep Vein Thrombosis. PE = Pulmonary Embolism. LMWH = Low molecular weight heparin. VTE = Venous Thromboembolism. OD = Once daily.

Study	Study design	Surgical approach	Primary outcome	Tumour site	VTE screening	Extended prophylaxis Regimen	Effect of extended prophylaxis	Conclusion
Schmeler et al. 2013 [61]	Observational retrospective	Open	VTE diagnosed within 30 and 90 days of surgery	Ovary= 354, Uterine=201, Cervix= 62, Vulva 17	No	Enoxaparin (40 mg) OD 28 days	VTE < 30 days 2.7% v 0.6% (P = 0.04). VTE < 90 days 3.7 vs 3.0% p = 0.619)	<ul style="list-style-type: none"> • Decreased VTE rate at 30 days • No effect on VTE rate at 90 days
Marques de Marino et al. (2018) [62]	Cohort study: Prospective extended prophylaxis cohort Retrospective comparator cohort	Open (n=389) Laparoscopic (n=107)	VTE diagnosed within 30 and 90 days of surgery	Ovary= 263 Uterine=226 Cervix= 82	Screening prior to randomisation and at 30 days post surgery in the extended prophylaxis cohort only	Enoxaparin (40 mg) OD 28 days	VTE < 30 days (1.9 vs 1.4%; p = 0.729), VTE<90 days (2.4% vs 2.5%; p=1.0).	<ul style="list-style-type: none"> • No effect on VTE rates at 30 and 90 days post surgery
Kim et al. (2017) [82]	Retrospective chart review	Robotic Surgery	Documented VTE within 30 and 60 days post surgery	Uterine n=403 (91% received extended prophylaxis)	No	LMWH (typically enoxaparin 40 mg) OD 30 days	VTE <30 days 2.80 v 0.5% (P = 0.25) VTE <60-days 5.6 v 0.8%, P = 0.07	<ul style="list-style-type: none"> • No significant effect on VTE rates
Carbajal-Mamani et al. (2020) [83]	retrospective cohort study	Robotic Surgery	Documented symptomatic VTE event within 30-days post surgery	Uterine n=132 (BMI>35)	No	Enoxaparin (40 mg) OD 28days	VTE < 30 days 1.6 v 0% P=0.1105	<ul style="list-style-type: none"> • No significant effect on VTE rates

complex surgery was associated with a clinically significant reduction of VTE from 6.6% preintervention to 2.7% post intervention with no difference in bleeding or infection rates [63].

Despite the strong recommendation for extended prophylaxis following pelvic-abdominal cancer surgery which includes

gynaecological cancer, uptake of extended prophylaxis has been low [64, 65]. Barriers to the use of extended prophylaxis include concerns regarding bleeding risk, physician willingness to change practice, patient compliance and financial cost [66,67]. A meta-analysis of 33 studies reported no difference in major bleeding or thrombocytopenia between

patients who received extended thromboprophylaxis and those who did not [68]. There was also no difference in patient preference and compliance between pneumatic stocking use and LMWH prophylactic therapy [69]. In a survey of 211 patients who were randomised to VTE prophylaxis with external pneumatic compression or LMWH, 78% were happy with LMWH and 74% preferred the pneumatic compression. Compliance was slightly greater in the LMWH arm at 92.2% while 90.4% complied with the external pneumatic compression [69]. In a similar study of patient experience and compliance with extended LMWH, high compliance with extended prophylaxis was reported however 86% of patients expressed a preference for a table form of prophylaxis provided it was as effective [70].

Financial burden is a major concern for some care providers. A study which calculated the cost effectiveness of thromboprophylaxis in gynaecological cancer patients [71] reported the average cost to diagnose DVT or PE ranged between \$361 and \$2185 depending on whether the patient required doppler ultrasound or Computed Tomographic Pulmonary Angiography (CTPA) with an estimated treatment cost of \$500 to include initial heparin doses, warfarin for 6 months and laboratory monitoring. On the other hand, in a 65 year old patient with advanced ovarian cancer at high risk for VTE, thromboprophylaxis use saved \$5132 per year of life [71]. Some might argue that unfractionated heparin is more cost effective than LMWH as thromboprophylaxis however [72] a study to determine patient cost and affordability showed that 90% refilled their prescription regardless of the cost [73] with an average cost of \$62; it was noted that cost was reduced following generic enoxaparin approval.

In addition to patient compliance, adherence to the guidelines is another issue. Despite knowledge and awareness of the high VTE risk in gynaecological cancer patients post-surgery, several studies have reported that a significant proportion of patients do not receive extended prophylaxis after discharge [64,74,75]. Reasons include lack of evidence of efficacy in the gynaecological cancer population [75], and a preference for using clinical judgment for prescribing VTE prophylaxis [64]. Computerised alert systems can assist in compliance and it was noted in one study that the VTE rate post cancer surgery has reduced by 41% at 90 days post-surgery in high risk patients following the introduction of an alert system [76].

1.6. MIS and VTE prophylaxis

Minimal invasive surgery is favoured over open surgery whenever it is feasible as it is associated with less blood loss, less postoperative complications, and faster recovery time [77]. As VTE risk in laparoscopic surgery is significantly less than open surgery [78] the value of thromboprophylaxis in laparoscopically treated patients has been questioned [79] with reported rate of VTE risk in cervical and endometrial cancer as low as 0.5% post laparoscopic surgery [80]. Guidelines recommended VTE prophylaxis post open and laparoscopic cancer surgery based on risk stratification [42,52] as cancer is a major risk factor for VTE, this means that laparoscopic surgery for cancer is included in the recommendation. In a randomised trial including 225 patients undergoing laparoscopy for colorectal cancer, 113 patients were randomised to short term prophylaxis and 112 to extended prophylaxis, 11 cases developed VTE, all in the short course arm suggesting that extended prophylaxis is warranted following laparoscopic surgery [81] (Table 1). There are no randomised trials in gynaecological cancer patients however several observational studies have reported on the use of extended prophylaxis post laparoscopic surgery (Table 2).

In a retrospective study of endometrial cancer patients undergoing robotic surgery there was no significant difference in the 30 and 60-day VTE rate following extended prophylaxis [82]. Other authors have suggested that even in patients with high BMI undergoing MIS, extended prophylaxis is not warranted [83]. A large Danish study showed that endometrial cancer was not an independent risk factor for VTE and similar rates of VTE were found post hysterectomy in patients with

benign and malignant disease [84].

During laparoscopic surgery, pneumoperitoneum up to 15mmHg is developed to get better access and visibility, this puts compression pressure on the vena cava and internal iliac veins and reduces venous return. The patient is also put in reverse Trendelenburg position; head down, to move the bowel out of the surgical field [85,86]. These steps increase venous stasis resulting in increased VTE risk. Pneumatic compression stocking use was found to overcome the stasis issue and is recommended in prolonged laparoscopic procedures [86]. In a retrospective randomised study to determine the efficacy of intermittent compression stockings in neutralising venous stasis [87] a 50–60% reduction of venous flow in the femoral vein during pneumoperitoneum and reverse Trendelenburg was found using intermittent compression to ankle, calf and thigh.

In a retrospective study of post-operative thromboprophylaxis in endometrial cancer patients [88], 558 patients were included, the majority (77%) of which were stage 1 and 80% were discharged within 24 hours following surgery. Patients were followed up for 90 days. There were no VTE events in the 88 patients who received extended thromboprophylaxis compared to 8 patients in the group who did not receive extended thromboprophylaxis. The study evaluated the cost of routine thromboprophylaxis at \$38 per patient and \$356 for extended thromboprophylaxis course. On the other hand, the cost of treating a VTE event was estimated as \$7653. The number needed to treat (NNT) was 58 to prevent one VTE event which questions the cost benefit of extended prophylaxis in this setting. It is likely that NNT would be lower in high risk patients which suggests that individual risk assessment is warranted.

There is a reluctance among physicians to prescribe extended prophylaxis for patients post laparoscopic surgery. In a survey done to evaluate the practice of thromboprophylaxis post laparoscopy among the members of the Society of Gynae-oncologists (SGO) 61.3% of the members believed that VTE risk post laparoscopic surgery was between 1–2%, 6.6% estimated it as 3–5% and 31% thought it was 0%. 51% of SGO members do not routinely give preoperative prophylaxis and discontinued post-operative prophylaxis after hospital discharge. Omission of prophylaxis was rare and was more common more older practitioners of 61–70-year age group [89].

1.7. Oral anticoagulants as prophylaxis following gynaecological cancer surgery

In recent years direct oral anticoagulants (DOACs) which directly inhibit coagulation factors have become available [90]. DOACs include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban which inhibit factor Xa. These drugs have significant advantages over heparin as they can be taken orally with no laboratory monitoring [91]. These anticoagulants have been shown to be safe and effective in the prevention and treatment of VTE in a variety of settings [91–93].

The efficacy of DOACs are not inferior to warfarin and enoxaparin in terms of VTE treatment and prophylaxis. In a randomised double-blind study, edoxaban was compared with warfarin as treatment for symptomatic thrombotic events [94]. Both drugs showed similar results however interestingly patients with pulmonary embolism and right ventricular dysfunction had a lower rate of VTE recurrence (3.3%) in the edoxaban arm compared with warfarin (6.2%), while risk of bleeding and coronary adverse events was similar in all groups. The RECORD study has showed that rivaroxaban is superior to enoxaparin as thromboprophylaxis post hip arthroplasty [95].

Less evidence is available for the use of DOACs as treatment and prophylaxis in the cancer population with bleeding risk a cause for concern. SELECT-D compared dalteparin and rivaroxaban as treatments for cancer patients with VTE [96]. There were fewer episodes of recurrent VTE associated with rivaroxaban, but there was an increase in the risk of bleeding. The results of this study are comparable to Hokusai trial [97] which reported that edoxaban had lower rate of recurrent venous

thromboembolism in cancer patients however the rate of major bleeding was higher with edoxaban compared with dalteparin. As most cancer patients are elderly with other medical comorbidities attention to drug - drug interaction and polypharmacy must be considered [98]. Prescribing DOACs along with non-steroidal anti-inflammatory drugs(NSAID), anti-platelet, serotonin-norepinephrine reuptake inhibitors (SNRI) & selective serotonin reuptake inhibitors (SSRI) may contribute to increase risk of bleeding [99].

In ambulatory patients undergoing chemotherapy, two recent trials (CASSINI and AVERT) assessed the use of DOACs for prophylaxis in patients receiving chemotherapy following risk assessment using the Khorana score. Both studies showed that apixaban and rivaroxaban were effective as thromboprophylaxis in intermediate/high risk patients [100, 101]. In a multicentre trial, 400 women with gynaecological cancer were randomised to apixaban or enoxaparin for total of 28 days postoperative prophylaxis. There was no difference between the two groups in terms of major bleeding, VTE events, patient adherence and quality of life [102]. Patients favoured apixaban as it was easier to take the medication and was associated with less pain. Glickman et al evaluated the cost effectiveness of DOAC versus LMWH as extended thromboprophylaxis in the same trial [103]. Cost-effectiveness was measured by incremental cost-effectiveness ratios (ICERs). ICERs were calculated as the difference in net cost between apixaban and enoxaparin per quality-adjusted life year (QALY) gained. Apixaban use resulted in 4.13 additional QALYs than enoxaparin. The net cost of apixaban was higher than enoxaparin for all individual events except DVT. Apixaban prescription resulted in the avoidance of 9.47 DVT events and 0.05 VTE-related deaths, while enoxaparin use was superior in the avoidance of 8.24 PE events. Despite the higher cost, apixaban was more cost effective in preventing DVT but not PE. It is noted that FDA approved of two forms of generic apixaban in January 2020, generic apixaban is likely to be available when the brand name expires in 2026.

1.8. Inferior Vena Cava filters

Inferior Vena Cava filters (IVCF) were first described in 1973 [104] by Greenfield, they were designed to prevent the propagation of thrombus from lower limb to the pulmonary vasculature. Among many indications for IVCF use, they can also be used in high risk patients who have a contraindication for anticoagulant medications due to risk of bleeding [105]. There is very limited data from randomised trials on the use of IVCFs. The PREPIC (Prévention du Risque d'Embolie Pulmonaire par Interruption Cave) study is the only long-term randomized study of filter placement in the prevention of PE [106]. Four hundred patients with proximal DVT with or without PE were randomized either to receive or not receive a filter in addition to standard anticoagulant treatment for at least 3 months, 56 patients had cancer. They concluded that IVCFs reduced the risk of PE from 15.1% to 6.2% but increased that of DVT and had no effect on survival. In another retrospective study [107] of 39 women evaluating use of IVCF prior to gynaecology cancer surgery, 35 women (90%) had a primary cancer diagnosis and 4 (10%) had recurrent disease. All mortality was cancer related and none was due to IVCF insertion. None of the women with an IVCF had progression of the thromboembolism and recent VTE diagnosis did not increase the surgical morbidity. In contrast, a retrospective study [108] on 115 cancer patients using IVCF reported that 66% had an adverse event, 52 patients died (45% of all patients), 8 of the deaths occurred after an additional thrombotic event. The American Society of Clinical Oncology guideline [53] advises against insertion of IVCF in patients with established or chronic thrombosis, or in patients with temporary contraindications to anticoagulant therapy (eg, surgery). The Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis [109] recommended against systematic insertion of IVCF in cancer patients with recurrent VTE, and that their use should be limited to situations where one or more strong contraindications to anticoagulation exist and the risk of potentially fatal PE is high. As there is no role for IVCF for

primary prevention or prophylaxis of PE or DVT, it may only be offered to patients with absolute contraindications to anticoagulant therapy in the acute treatment setting e.g., VTE diagnosis within the past 4 weeks if the thrombus burden was considered life-threatening.

1.9. Additional measures which may reduce the risk of VTE

Enhanced recovery program or fast track surgery is a term introduced in the 1990s by Professor Henrik Kehlet [110]; it states that surgical stress mediated by trauma induced endocrine metabolic changes is a key factor for postoperative morbidity. The program starts preoperatively and continues postoperatively, involves no bowel preparation and encourages 4hr post-operative high protein diet, preoperative thromboprophylaxis, pain optimisation, early mobilisation, and hospital discharge. There is a shortage of randomised controlled trials to accurately assess the effectiveness of these programs however promising results are emerging from the available studies [111]. In a study comparing perioperative outcome in ovarian cancer patients, conventional care was compared with, fast-track rehabilitation with a planned care program including continuous epidural analgesia, early oral feeding, and mobilization [112]. Although VTE rates were not assessed, patients on fast track were discharged earlier which may reduce VTE risk. In a meta-analysis of 31 studies including 5 randomised trials accessing the benefit of enhanced recovery after gynae-oncology surgery (ERAS) [113], hospital stay was reduced by an average of 1.6 days with no increase in readmission rate or mortality in gynae-oncology patients. This evidence supports implementation of ERAS as standard of care in gynae-oncology.

Implementation of prehabilitation programs (PREHAB) [114] (physical and psychological assessment of the patients preoperatively), improves surgical outcome and reduces morbidity. These programmes may also improve VTE rates post-surgery yet more controlled trials are needed as limited data is available on gynaecological cancer patients. Obesity is a major risk factor for both VTE and endometrial cancer. Individualised exercise programmes in women undergoing endometrial cancer surgery improve quality of life [115]. Exercise was safe in this group and should be encouraged. PREHAB following ERAS protocol in ovarian cancer patients undergoing surgery is currently being evaluated [116].

2. Conclusion

Extended prophylaxis is safe and cost-effective post laparotomy in gynaecological cancer patients. Although guidelines also recommend extended prophylaxis for cancer patients post MIS, observational studies suggest that the rate of VTE following MIS in gynaecological cancer patients is low and randomised trials in this setting are lacking. Due to the low incidence of VTE in patients undergoing MIS, large randomised trials would be required to support and justify use in laparoscopy and robotic gynaecological cancer surgery. In the absence of this data, individual risk stratification may help identify patients who would benefit from extended prophylaxis. Although evidence is lacking, direct oral anticoagulants may play a role in extended prophylaxis post cancer surgery in the future. Improved surgical techniques and enhanced recovery programmes may also modify VTE risk.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Feras Abu Saadeh and Dr. Lucy Norris have received unrestricted educational grants from Leo Pharma

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